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FUNCTIONAL RECOVERY AFTER TRAUMATIC SPINAL NERVE ROOT (BRACHIAL PLEXUS) INJURY IN MAN

Thesis submitted for the degree of Doctorate of Medicine

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Declaration

I confirm that this is my own work and properly and fully acknowledged.

Abstract

In this work, the functional consequences of segmental spinal cord regeneration and plasticity after spinal cord nerve root injury and repair in humans were studied. Spinal nerve root avulsions occur particularly in brachial plexus traction injuries. Models of spinal cord regeneration and functional recovery in patients with spinal root avulsion were developed and changes in motor, sensory and autonomic functions in patients with severe brachial plexus injury studied with clinical and neurophysiological techniques. Regeneration of long fibre tracts and /or segmental connections was assessed. Patients were recruited at RNOH, Stanmore, and patient studies performed at the Hammersmith Hospital.

Fifty one patients who had sustained, total brachial plexus injury with spinal nerve root avulsion repaired by various surgical strategies were assessed for recovery of motor function and motor phenomena (co-contraction and "breathing arm"). The results demonstrate that, following re-connection of avulsed spinal roots to the spinal cord, injured motor neurons can regenerate from the CNS to the periphery with functional recovery. The outcome was similar to that for conventional repair of a less severe brachial plexus injury.

Seventy six patients who had sustained brachial plexus injury were studied for sensory and pain phenomena at different time points after injury. Pain was assessed by direct interview using pain questionnaires. Different sensory modalities in affected dermatomes showed very poor or no recovery. This study concluded that, due to the complexity of the sensory system, recovery of sensory function depends not only on technically successful nerve repair but also on CNS plasticity. It was found that patients without any surgical repair suffered the worst pain and its severity is least in the patient group repaired by graft or other nerve transfer.

Acknowledgements

I have become indebted to many people during the completion of this thesis. I would like to thank my supervisors Professor T Carlstedt and Dr P Misra for their supervision and guidance on this work. I would also like to thank Professor P Anand and Professor R Birch for their support, guidance and teaching through out this work.

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This thesis is dedicated to my parents.

Contents

FUNCTIONAL RECOVERY AFTER TRAUMATIC SPINAL NERVE ROOT (BRACHIAL PLEXUS) INJURY IN MAN

List of figures

List of tables

List of commonly used abbreviations

C	Cervical segment
CDT	Cool Detection Threshold
CNS	Central Nervous System
CT	Computed Tomography
EMG	Electromyography
MEP	Motor evoked potential
MPQ	McGill Pain Questionnaires
MRI	Magnetic Resonant Imaging
MUP	Motor Unit Potential
NCS	Nerve conduction studies
PNS	Peripheral Nervous System
QST	Quantitative Sensory Testing
SC	Spinal cord
SEP	Somatosensory evoked potential
T	Thoracic segment
TMS	Trans Cranial Magnetic Stimulation
VAS	Visual Analogue Scale
WDT	Warm Detection Threshold

Chapter I: Introduction & Literature Review

1.1. Introduction

1.1.1. Impact of the brachial plexus injury

Nerve root avulsions from the spinal cord occur in humans particularly in brachial plexus traction injury. Road traffic accidents or incidents which occur during complicated births are the most common causes of such injuries. Traumatic brachial plexus injury occurs mainly in fit young men as a result of motor cycle accidents (Alnot, 1995; Birch, 1992; Nagano, 1998). Usually, both the ventral and dorsal roots are involved, and the patient is subjected to paralysis and sensory dysfunction with numbness in the limb in conjunction with extreme, almost unbearable, intractable pain (Berman *et al.*, 1998; Birch *et al.*, 1998). These lesions have been considered as unfavourable and devastating with regard to both survival and regeneration of injured neurons. The consequences of such injuries can be profound and there is a grave impact on physical, mental, psychological and social well being of the patients. There are at least three publications describing the natural history of severe brachial plexus lesions without surgical nerve repair and showing that there was only unfavourable functional recovery in a few patients (Birch *et al.*, 1998). The incidence of traumatic brachial plexus injury appears to be increasing which could be due largely to improved survival in patients with other, more severe injuries (Birch, 2003). More than five hundred adults per year in Britain suffer permanent disability from traction brachial plexus injury (Goldie and Coates, 1992) the majority of which are due to road traffic accidents (Birch *et al.*, 1998). Management of patients with such injuries is complex and often incomplete (Birch, 2003).

1.1.2. A historical overview of brachial plexus surgery

Injuries to the brachial plexus are the worst of all peripheral nerve lesions. A vivid description of the effects of traumatic brachial plexus injury is given in the eighth book of Homer's Iliad (Homers, 2003) and possibly the first medical report in literature alluding to the diagnosis and treatment of brachial plexus injury was mentioned in an episode of the life of the Roman physician Galen (Robotti *et al.*, 1995). Subsequently, other European anatomists contributed to the understanding of brachial plexus injury during the Renaissance. However, it is only by the eighteenth century that a full

description of a brachial plexus lesion was found (Robotti *et al.*, 1995). The French physician Flaubert in 1827 reported the first autopsy case of a traction injury to a spinal nerve root (Holtzer *et al.*, 2002; Robotti *et al.*, 1995). Surgical treatment for such an injury was attempted by the late nineteenth century and the first account of suture in brachial plexus injury was published by Thoburn of Manchester in 1896 (Thoburn, 1900). At the beginning of the 20th century, the technique of neurotization or nerve transfer to repair brachial plexus injury was attempted by the British neurologists Harris and Low, then followed by the American surgeon Tuttle (Harris, 1903; Tuttle, 1913). The first intraspinal exploration of avulsion injury was performed by Frazier and Skillern ((Frazier and Skillern, 1911). First and Second World Wars provided much opportunity to surgeons for repairing nerve injury. However, until the Second World War, the surgical repair of the brachial plexus was uncommon and most surgeons practiced "a wait and see'' policy (Kawai, 2000; Robotti *et al.*, 1995). The Medical Research Council asked Seddon and colleagues to study peripheral nerve lesions and by 1954, their report concluded that operative repair had little value except probably in lesions of the upper trunk (Seddon, 1954). This pessimistic outlook was shared worldwide (Birch *et al.*, 1998; Robotti *et al.*, 1995) and surgical repair of the injury was regarded as unfavourable and unrewarding (Bonnard and Narakas, 1995; Kawai, 2000). However, since the early 1970s, useful results have been observed after surgical repair possibly because of the considerable advances in the understanding of traction brachial plexus injury in adults leading to accurate diagnosis and the development of refined microsurgical techniques (Birch, 2003; Sunderland, 1978). Such progress, over the past five decades by Seddon, Brooks, Barnes, Bonney, Narakas and many others have led to dramatic changes in the management of traction brachial plexus injury (Parry, 1995). It is now standard practice to repair brachial plexus lesions (Birch, 2001; Rutowski, 1993). In 1980, Jamieson and Eames investigated the regeneration of axons through re-attached ventral roots in dogs (Jamieson A, 1980). Prompted by these earlier attempts, Carlstedt and colleagues performed a lengthy series of laboratory investigations in several species including primates, which demonstrated an unexpected capacity of motor neurones for cell survival and regeneration within the central nervous system after re-implantation of avulsed ventral roots to the spinal cord (Carlstedt, 1997; Carlstedt *et al.*, 1993;Carlstedt *et al* 1986 ;Cullheim *et al.*, 1989; Smith and Kodama, 1991;Hallin *et al.*, 1999). Subsequently, a surgical re-implantation technique to attempt to restore function after ventral root avulsion injuries in man was introduced (Carlstedt *et al.*, 2000; Carlstedt *et al.*, 1995). A follow up study of the first ten re-implanted cases showed that three

patients regained some useful function (Carlstedt *et al.*, 2000). There is no doubt that functional recovery from the central nervous system to peripheral nervous system is possible and this novel technique would be the way forward in the treatment of very severe brachial plexus traction injury i.e. multiple nerve root avulsions.

1.2. Organisation and Anatomy of the nervous system

1.2.1. Organisation of the nervous system

Anatomically, the nervous system consists of peripheral nerves, the spinal cord and the brain. In other words, the nervous system can be divided into a central and peripheral nervous system. The central nervous system consists of the brain and the spinal cord and the peripheral nervous system consists of the cranial and the spinal nerves.

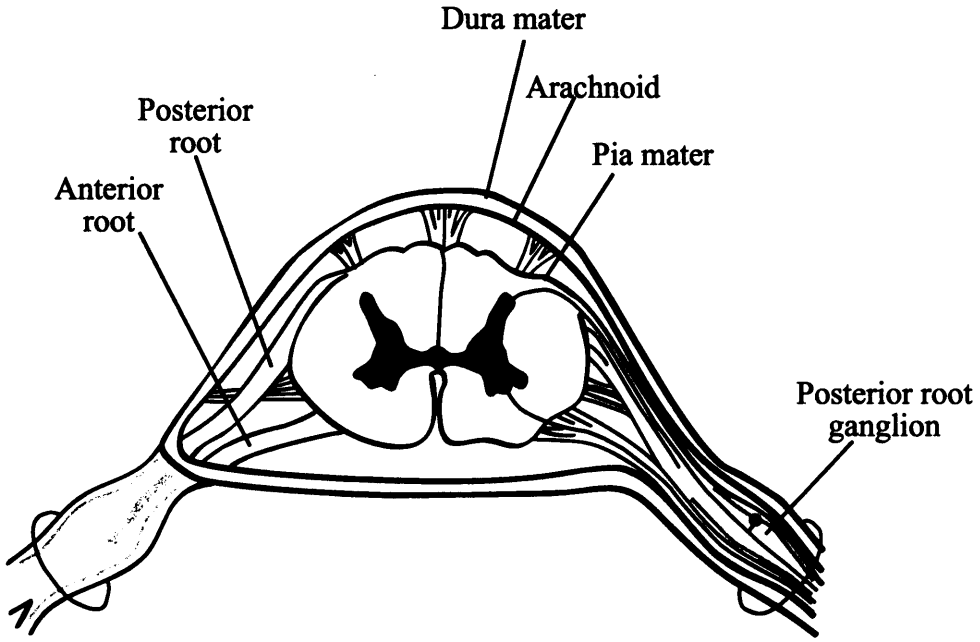
1.2.2. The Peripheral nervous system

The central nervous system controls the body via the peripheral nervous system which consists mostly of cranial and spinal nerves. Peripheral nerves contain motor, sensory and autonomic nerve fibres.

Spinal nerves

Of the 31 pairs of spinal nerves, there are usually 8 cervical, 12 thoracic, 5 lumber, 5 sacral and 1 coccygeal arising from the spinal cord. Each spinal nerve leaves or enters the spinal cord by an anterior, largely motor, root and posterior, sensory root Figure1.1. Each sensory root splits into several rootlets as it approaches the spinal cord, then enters the spinal cord along the line of postero-lateral sulcus. The division of the anterior roots into rootlets is less obvious and takes place nearer the cord. The nerve cell bodies of the fibres forming the anterior roots are mostly situated in anterior horn of the grey matter of the spinal cord and those of fibres in posterior roots are in root ganglia, situated in the or near the intervertebral foramen.

Figure 1.1. The origin of the roots from the cord, their junction just distal to the posterior root ganglion, and the emergence of the nerve from the spinal canal.
(Pictures taken from Birch, Bonney, Wynn-Parry. Surgical disorders of the peripheral nerves: Churchill Livingstone, 1998 with permission).



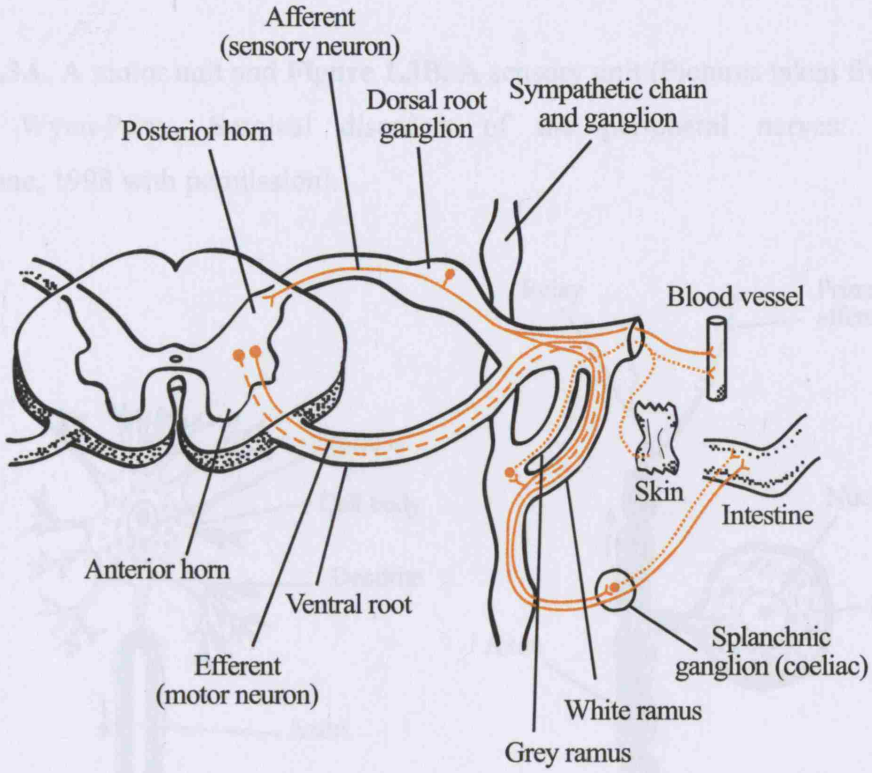
Autonomic nervous system

The autonomic nervous system is divided into two systems- the sympathetic and parasympathetic nervous system innervating the viscera, blood vessels, sweat gland and erector pilorum.

Sympathetic nervous system

The preganglionic cells of the efferent fibres of the sympathetic system are situated in the lateral part of the grey matter of the spinal cord from the first thoracic to second lumbar level. The ganglia are in the para vertebral sympathetic chains which extend along the side of spinal cord. The head and neck are supplied by the uppermost three thoracic segments. Nerves supplying the dilator of the pupil and levator palpabrae superioris muscles are mainly from the first thoracic segment. The sympathetic supply to the upper limb arises mainly from the second to sixth thoracic segments Figure 1.2.

Figure 1.2. Efferent and afferent autonomic paths in the spinal cord and ganglionic chain (Pictures taken from Birch, Bonney, Wynn-Parry. Surgical disorders of the peripheral nerves: Churchill Livingstone, 1998 with permission).



Parasympathetic nervous system

The efferent outflow of the parasympathetic nervous system arises from nuclei in the mid brain, hind brain, brainstem and sacral part of the spinal cord. The ganglia of the parasympathetic nervous system are located in or near the organ they supply.

1.2.3. Microanatomy of the peripheral nerve

The peripheral nerve is composed of numerous fibre types that convey electrical impulses to and from the central nervous system. Detailed description of the peripheral nerve anatomy and function is available elsewhere. The neuron is a unique cell with cell body and axon which is either myelinated or unmyelinated. Myelinated axons are surrounded by Schwann cells arranged in a longitudinal continuous chain to form a myelinated nerve fibres but an unmyelinated axon is associated with only one Schwann cell (Flores *et al.*, 2000). Individual nerve fibres (myelinated and unmyelinated) are organised in bundles called fascicles and enveloped by a membrane, the perineurium. The fascicles usually are organised in groups, held together by connective tissue called

epineurium. Between the nerve fibres and their basement membrane is intra-fascicular connective tissue known as the endoneurium. Peripheral nerves have a well developed microvascular system with vascular plexuses in all their layers of connective tissue (Lundborg, 1975).(Fig 1.3-1.5)

Figure 1.3A. A motor unit and **Figure 1.3B.** A sensory unit (Pictures taken from Birch, Bonney, Wynn-Parry. Surgical disorders of the peripheral nerves: Churchill Livingstone, 1998 with permission).

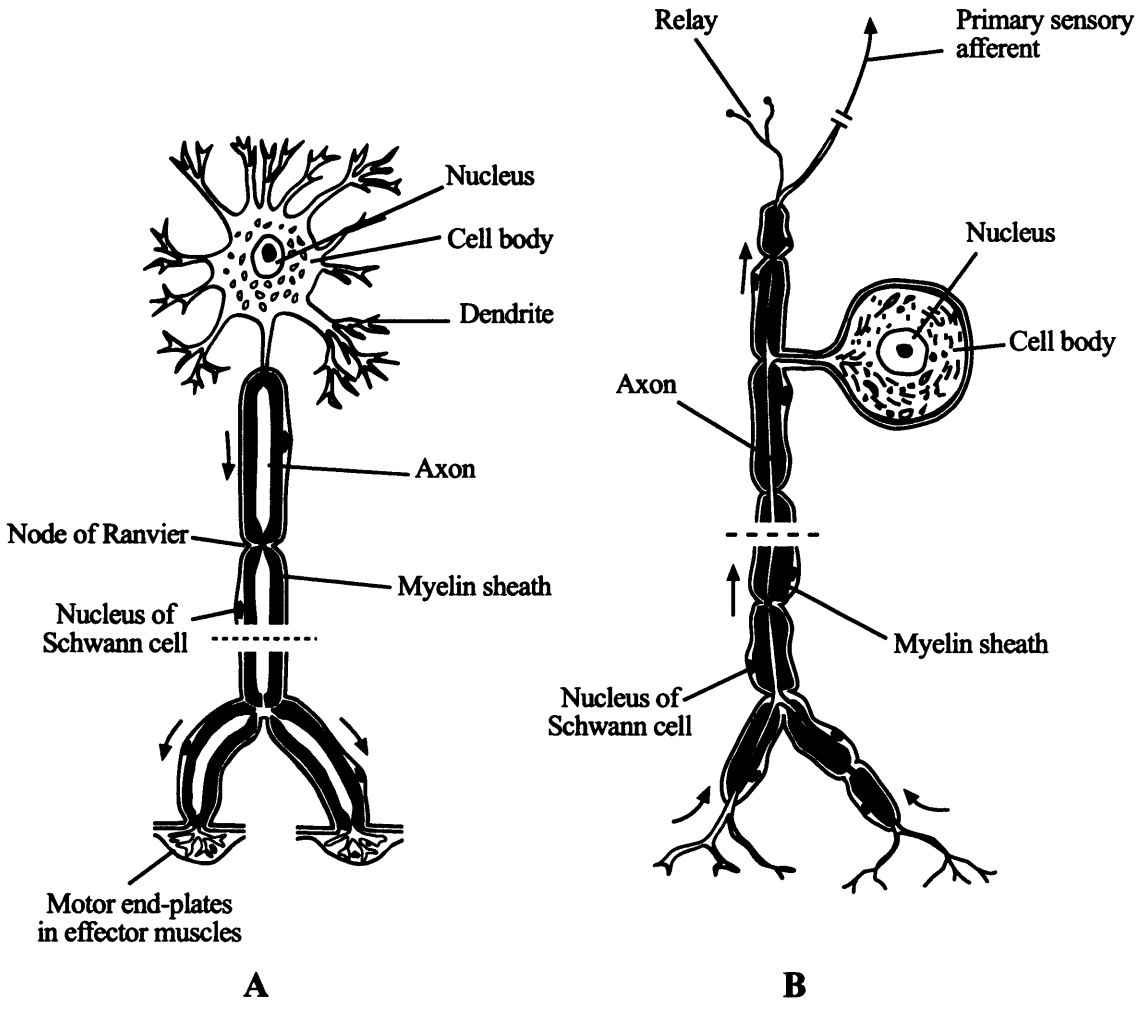


Figure 1.4. Fascicular arrangement of nerve fibres; supporting structures and Schwann cell apparatus in myelinated and unmyelinated fibres (Pictures taken from Birch, Bonney, Wynn-Parry. Surgical disorders of the peripheral nerves: Churchill Livingstone, 1998 with permission.).

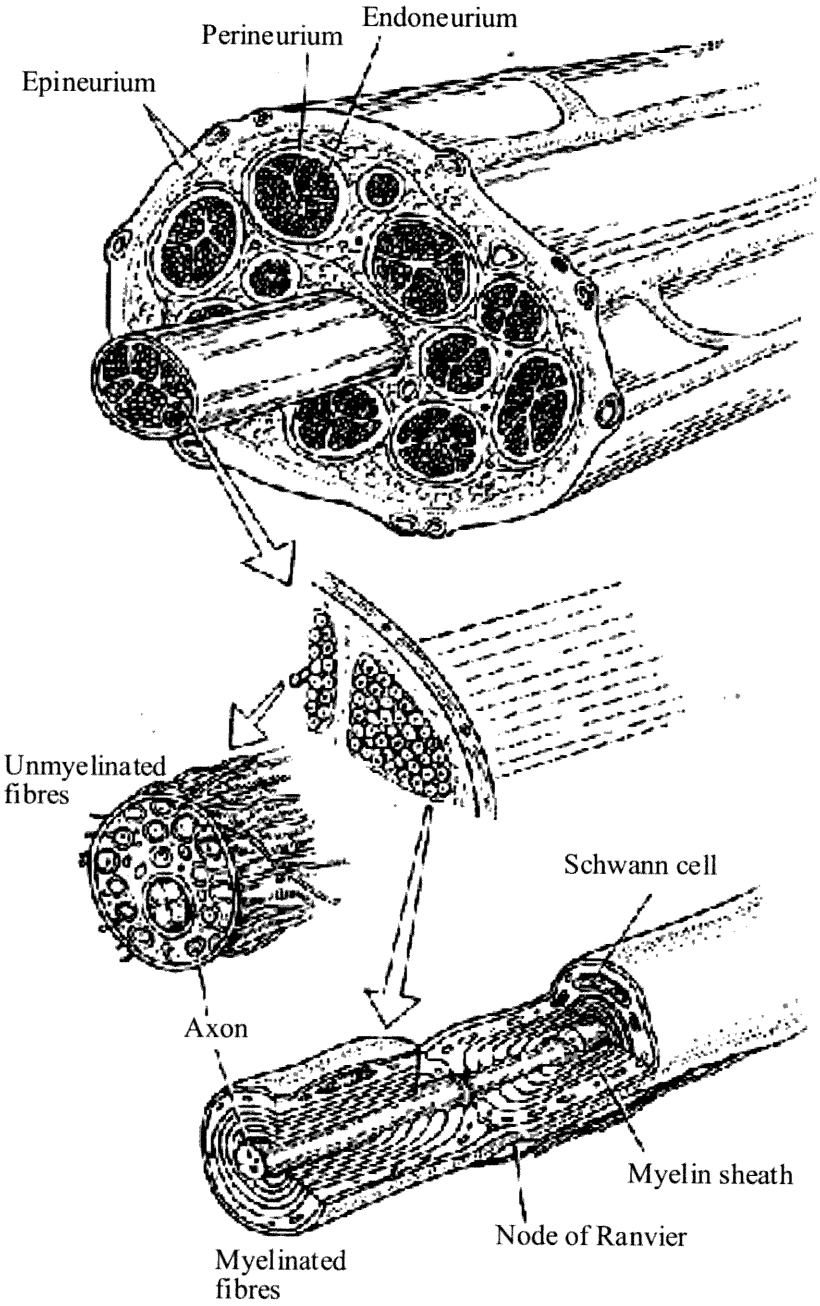
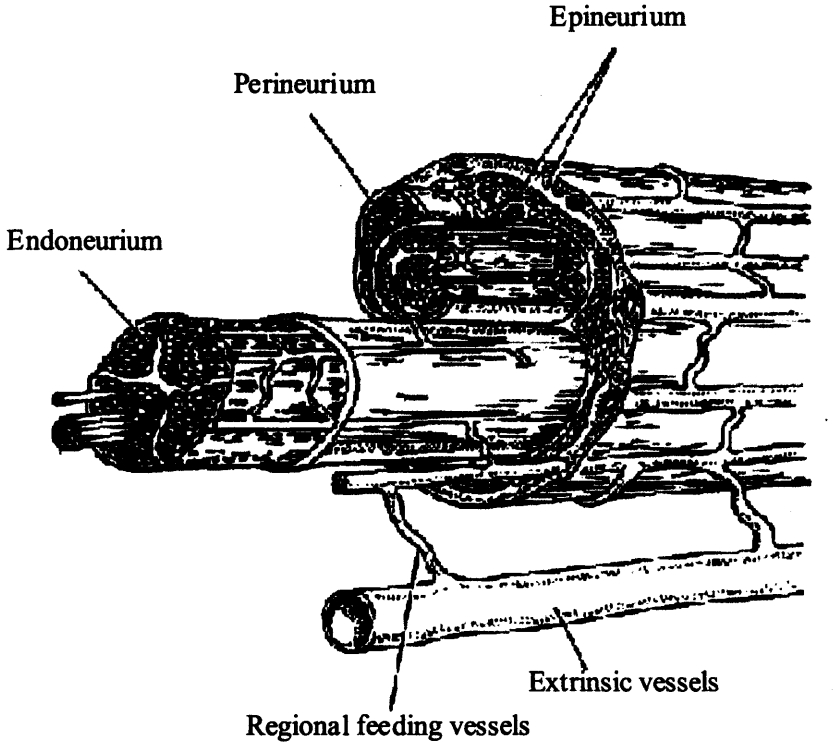


Figure 1.5. The vascular system of the peripheral nerve. (Pictures taken from Birch, Bonney, Wynn-Parry. Surgical disorders of the peripheral nerves: Churchill Livingstone, 1998 with permission.).



Peripheral nerves are motor, sensory or autonomic each having specific characteristics. Motor nerve fibres arise from neurons located in the anterior horn of the spinal cord. The efferent endings of motor nerve fibres terminate on motor units within the periphery at the neuromuscular junction. The numerous types of sensory nerve endings located in the periphery include mechanoreceptors responsible for the pressure and proprioceptive information, and nociceptors, thermoreceptors, and chemoreceptors, which together are responsible for temperature and pain information. Sensory fibres are also present in motor nerves. Motor and cutaneous nerves contain many different nerve fibres and these are classified into different subgroups Table 1.1.

Table 1.1. Nerve fibres types (modified from Review of Medical Physiology edited by W F Ganong; Appleton and Lange,1993).

Classification of fibre type		Function	Fibre diameter (μm)	Conduction Velocity (m/s)
Ia and Ib	A α	Proprioception; somatic motor	12-20	70-120
II	A β	Touch, pressure	5-12	30-70
II	Aγ	Motor to muscle spindles	3-6	15-30
III	Aδ	Pain, cold, touch	2-5	12-30
	B	Preganglionic autonomic	<3	3-15
IV	C	Pain, temperature, some mechanoception, reflex responses	0.4-1.2	0.5-2
	C	Postganglionic sympathetic	0.3-1.3	0.7-2.3

A and B fibres are myelinated; C fibres are unmyelinated.

1.2.4. The Central Nervous System

The central nervous system consists of the brain and the spinal cord. Detailed description of the functional and anatomical organization of the brain can be read in any standard text book and hence only relevant will be mentioned in this chapter.

Motor Cortex and Somatosensory Cortex

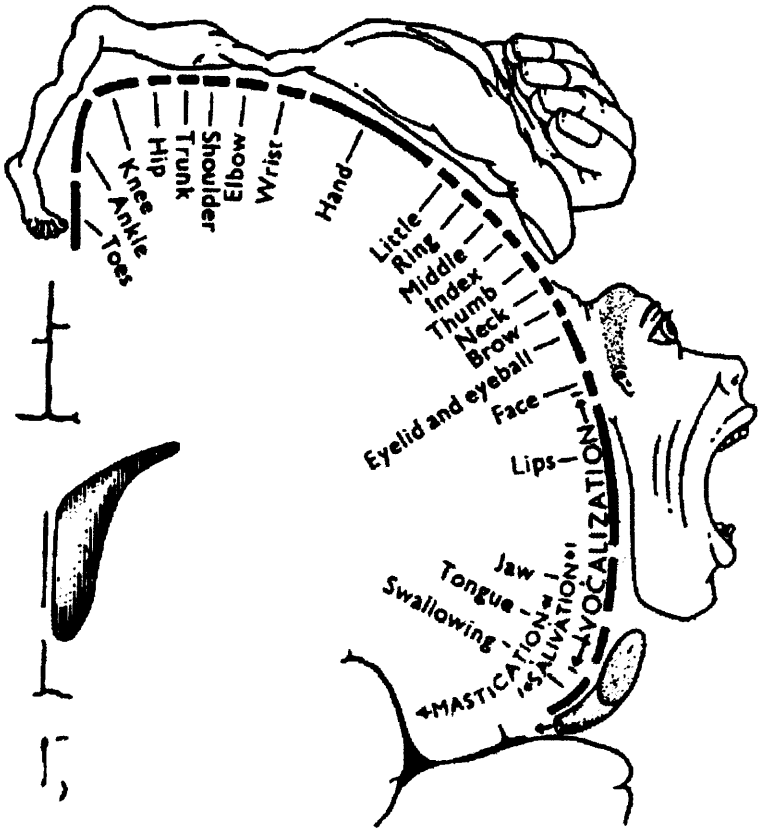
In 1823, the French physiologist Marie-Jean Pierre attempted to identify the function of different parts of cerebral hemisphere using experimental ablation methods and concluded that the cerebrum is involved in sensation and perception. In 1870, German physiologists, Gustav Fritsch and Eduard Hitzig demonstrated that applying small electrical currents to a circumscribed area of the exposed surface of the brain of a dog could produce discrete movements and the Scottish Neurologist David Ferrier repeated these experiments with monkeys. Furthermore, in 1881, he proved that removal of the same region of cerebrum causes paralysis. From the 1930s to 1950s, the Canadian neurosurgeon Wilder Penfield and Theodore Rasmussen of McGill University studied meticulously the localisation of the somatosensory system. They used electrical stimulation of various areas of the human brain during operation under local anaesthesia (Penfield Wilder and Rasmussen, 1957). Their invaluable work laid the foundation for the understanding of the organisation of the nervous system.

Motor Cortex

The motor cortex is situated in the frontal lobe. Although it controls movement, the control of voluntary movement engages almost all areas of the cortex because directed movement depends on spacial orientation with plan to get it there etc. A somatotopic organisation of the human motor cortex is shown in Figure 1.6.

The brain communicates the motor neuron of the spinal cord via the corticospinal tract, which is involved in the voluntary movement of the musculature. Axons, originating from the cortex, descend through the lateral path way of spinal cord. At the junction of the medulla and spinal cord, the corticospinal tract decussates.

Figure 1.6. The motor homunculus showing proportional somatotopical representation in the main motor area. After Penfield and Rasmussen 1950.

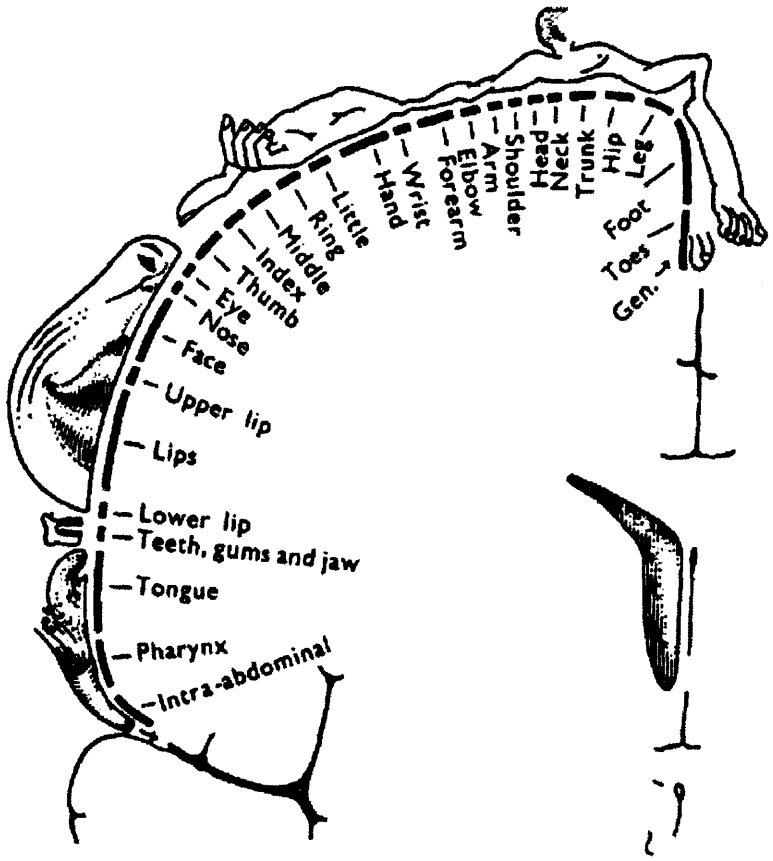


Somatosensory Cortex

The most complex sensory processing occurs in the cortex. Most of the cortex concerned with the somatic sensory system is in the parietal lobe. The primary somatosensory cortex (S1) occupies the postcentral gyrus of the parietal lobe and is organised in a somatotopic pattern like motor cortex. Figure 1.7.

The primary somatosensory cortex receives dense inputs from the ventroposterolateral (VPL) and venteroposteromedial (VPM) nuclei of the thalamus and its neurons are very responsive to somatosensory stimuli. Axons from the dorsal nuclei of the spinal cord terminate at the VPL and anterolateral funiculus of the spinal cord terminate in several thalamic nuclei including the VPL nucleus. Neurons in the ventral posterior parts of thalamus are also topographically organised.

Figure 1.7. The sensory homunculus showing proportional somatotopical representation in the main sensory area. After Penfield and Rasmussen 1950.



Brainstem

The brainstem connects brain and spinal cord. The brainstem also contains a group of nuclei, namely the nucleus cuneatus, nucleus gracilis and spinal trigeminal nucleus, which are important for the transmission of somatosensory information. The ascending sensory neurons of the dorsal nuclei of the spinal cord relay at the nucleus cuneatus, nucleus gracilis and then ascend to the contralateral thalamus. Many neurons of the

anterolateral funiculus of the spinal cord terminate in the reticular formation but some of them terminate in thalamus.

Many brainstem nuclei mediate simple reflexes similar to those of the spinal cord and extensive connections of the neural circuit of the brainstem are responsible for more complex functions which are essential for life such as respiration and consciousness.

Spinal cord

The spinal cord is encased in the bony vertebral column that extends from the brain stem to the Conus medullaris. The spinal cord contains a neural circuit that performs tasks related to motor and sensory functions. Thirty one pairs of spinal nerves that arise from the spinal cord impose a segmental organisation of the spinal cord. Spinal nerves communicate with the brain and brainstem via the descending and ascending tracts of the spinal cord.

Segmental (Transverse) organisation of the spinal cord

The spinal cord varies in diameter throughout its length according to the number of neurons that supply different parts of the body. The diameter of the cord is wider in the cervical and lumbar regions because of the rich innervation to the limbs. The core of the spinal cord is grey matter consisting of neuronal cell bodies and is sub-divided into dorsal, ventral and lateral horns. The neurons from the grey matter receive afferent projections from the dorsal root ganglia and other parts of the central nervous system. It also innervates peripheral targets such as muscle and autonomic ganglia. The central grey matter is surrounded by outer white matter consisting of long axons that form the descending and ascending tracts. The white matter is divided into 3 columns- the dorsal, ventral and lateral columns.

Descending and ascending tracts of the spinal cord (Longitudinal organisation of the spinal cord)

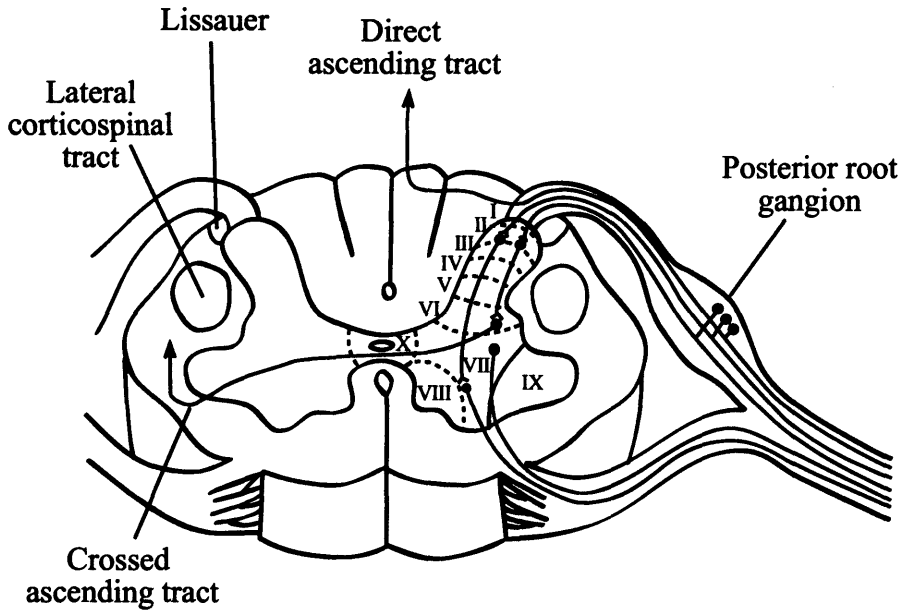
Many parts of the brain send descending tracts to the spinal cord and among them corticospinal tract is a major tract controlling voluntary movement as mentioned above. The corticospinal tract descends along the lateral funiculus of the spinal cord and its fibres are topographically organised. All somatosensory sensations that reach consciousness ascend via a pathway through dorsal column-medial lemniscus or spinothalmic tract at the anterolateral column. The former is concerned with carrying

sensations regarding touch, vibration sensation, tactile discrimination, and proprioception and the latter mediates pain and temperature sensation.

Cytoarchitecture of the central grey region

In 1952, Rexed discovered and introduced a laminar classification system of the spinal cord (Rexed, 1954). The dorsal horn is composed of Rexed I-VI and each layer is composed of different types of neuron concerned with sensation and pain. The anterior horn is composed of Rexed VII-IX and concerned with movement and movement associated reflexes. Figure 1.8.

Figure 1.8. The laminae of the grey matter, with direct ascending, cross ascending and interneural tracts (Pictures taken from Birch, Bonney, Wynn-Parry. Surgical disorders of the peripheral nerves: Churchill Livingstone, 1998 with permission).



1.2.5. Spinal cord in relation to the peripheral nervous system: Transitional Region

There are profound differences between the spinal cord and peripheral nerves in terms of their development, structure, organisation and function as well as their reaction to injury. All of the nerve fibres in the peripheral nervous system (PNS), except for those extending from the postganglionic autonomic neurons, are also partly located in the central nervous system (CNS). Given the large difference in organisation between the

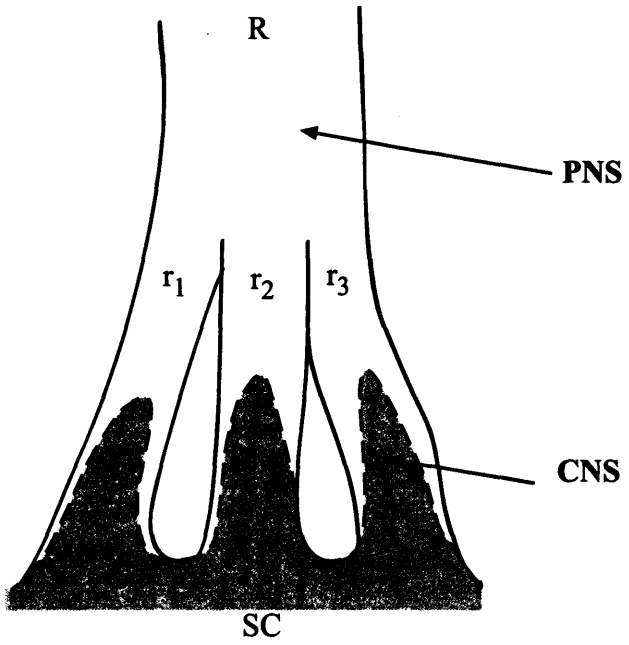
two compartments, most nerve fibres in the PNS show profound transformation when entering the CNS compartment. The segment of the spinal nerve root situated closest to the spinal cord, i.e. root at spinal cord junction, consists of a specific and specialised part of the nervous system where most transformation between the peripheral nerves and spinal cord occurs. This region is referred to as the ''transitional region (TR)'', the most proximal free part of the root which is one and the same cross section contains both CNS and PNS tissue (Carlstedt *et al.*, 2004). The contour of the CNS-PNS junction is usually dome shaped with a peripherally orientated convexity. Figure 1.9.

When following the TR in serial sections centrally, the outer zone eventually transforms into the glial fringe zone as it acquires an addition of glial processes emanating from the CNS. The astrocytic processes are arranged in bundles covered by basement membrane. At a distance of 5 to 20 μm from the borderline the individual members of the glial fringe unite outside myelinated nerve fibres, separating them and enclosing them in a tube- of a holster-like fashion. At the end of a cul-de-sac the basement membrane often shows defects, through which endoneurial collagen may pass for a distance of several micrometers into the CNS extracellular space. Unmyelinated fibres are often found in a creeper –like manner along the astrocytic processes. The familiar cell types observed in the PNS compartments are Schwann cells, fibroblast, pericytes and a group of unclassified cells. The mantle zone is a continuation of the external glial limiting membrane and has a high content of astrocytic nuclei (Berthold *et al.*, 1993).

At some distance from the CNS/PNS junction, unmyelinated axons of the PNS begin an extensive redistribution, including Schwann cell alterations and changes of position in relation to the central axis of the individual rootlets. As a result of rearrangements, unmyelinated and small myelinated fibres come to occupy preferentially the ventrolateral aspect of the rootlet at the level of junction with the spinal cord. The shorter internuclear distance and small number of axons per Schwann cell give a comparatively high number of Schwann cell nuclei per unit length of unmyelinated axons in the TR. Internodal length of myelinated nerve fibres is shorter in the TR than further distally in the root. The number of myelin lamellae is usually higher in the CNS than in the PNS part of the same fibre (Berthold *et al.*, 1993).

In conclusion, when comparing PNS and CNS structure, the PNS tissue is characterised by axon-Schwann cell units demarcated by basement membrane in a collagen rich extracellular endoneurial space. In the CNS tissue, the extracellular space is exceedingly small, collagen is lacking, and the axons are embedded in a complex network of oligodendrocyte and astrocytic processes (Carlstedt *et al.*, 2004).

Figure 1.9. The transition zone between the central and peripheral nervous system. R, root;r1- r3, rootlets; SC, spinal cord, PNS; peripheral nervous system, CNS; central nervous system (Pictures taken from T Carlstedt *et al.* The human nervous system: Elsevier Academic Press, 2004 with permission).



1.3. Structure of the brachial plexus

1.3.1. Anatomy of the brachial plexus

The brachial plexus is one of the largest and most complex peripheral nervous system structures, consisting more than 100,000 axons (Wilbourn, 2002), supplying most of the upper extremities and shoulder. The brachial plexus is a triangular shaped structure extending from the spinal cord to the axilla, measuring an average length of 15.3 cm in man (Ferrante, 2004). Brachial plexus has five components: five roots, three trunks, six divisions, three cords and a variable number of terminal nerves. The size, superficial location, and position of the brachial plexus, between two highly mobile structures, the neck and upper extremity allows an increased vulnerability to trauma (Ferreira *et al.*, 1998). (Fig. 1.10- 1.12).

Figure 1.10. The relationship of the brachial plexus to axial skeleton, the forequarter and the arm. (Pictures taken from Birch, Bonney, Wynn-Parry. Surgical disorders of the peripheral nerves: Churchill Livingstone, 1998 with permission.).

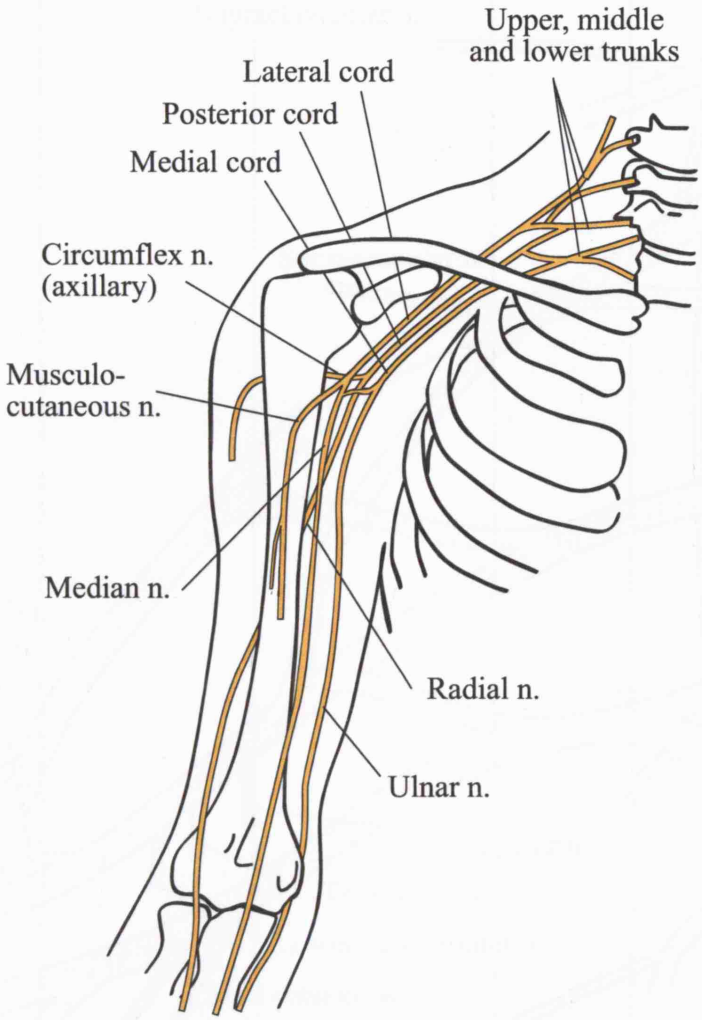


Figure 1.11. The sequence of brachial plexus. The anterior primary rami; trunks; division; cords; nerves. (Pictures taken from Birch, Bonney, Wynn-Parry. Surgical disorders of the peripheral nerves: Churchill Livingstone, 1998 with permission).

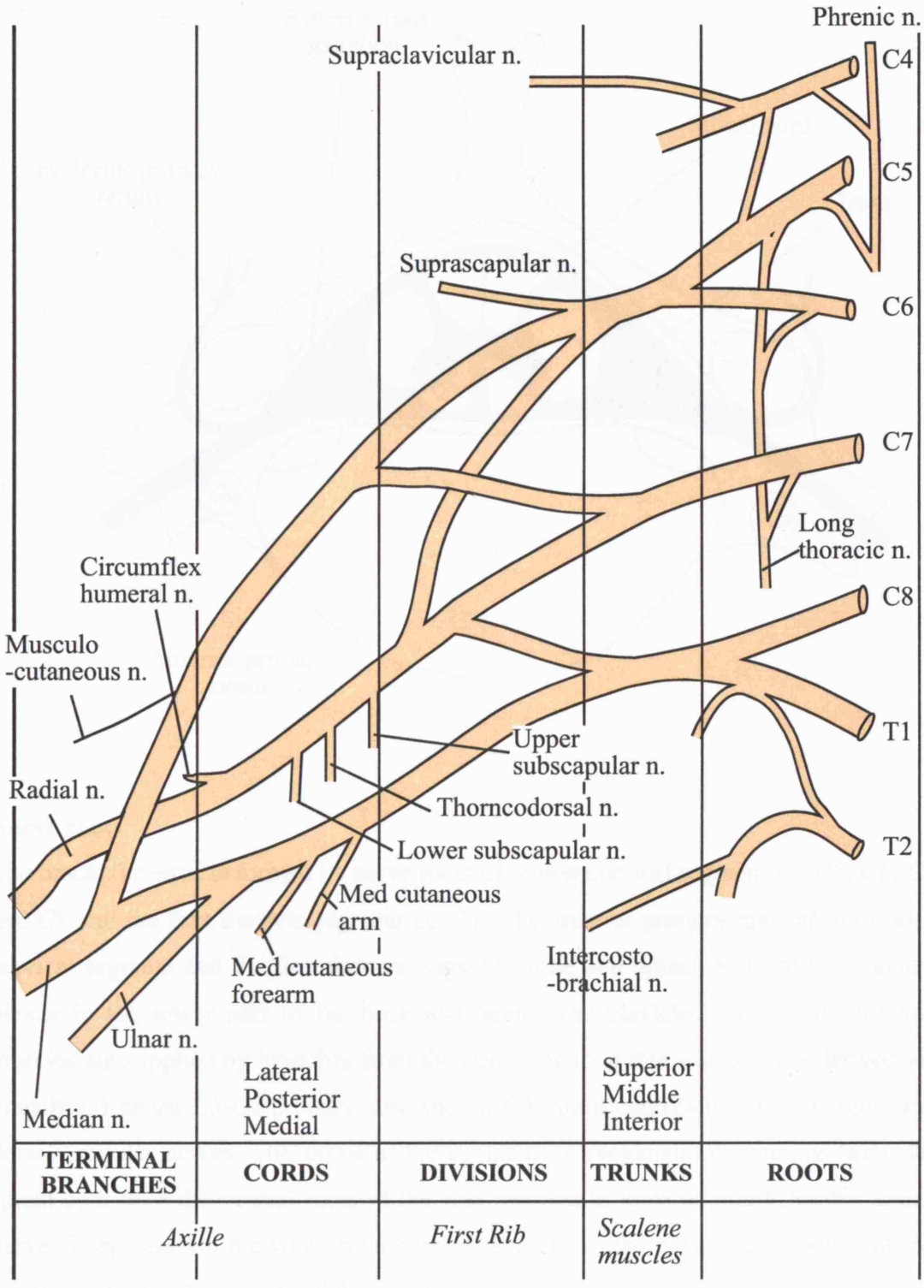
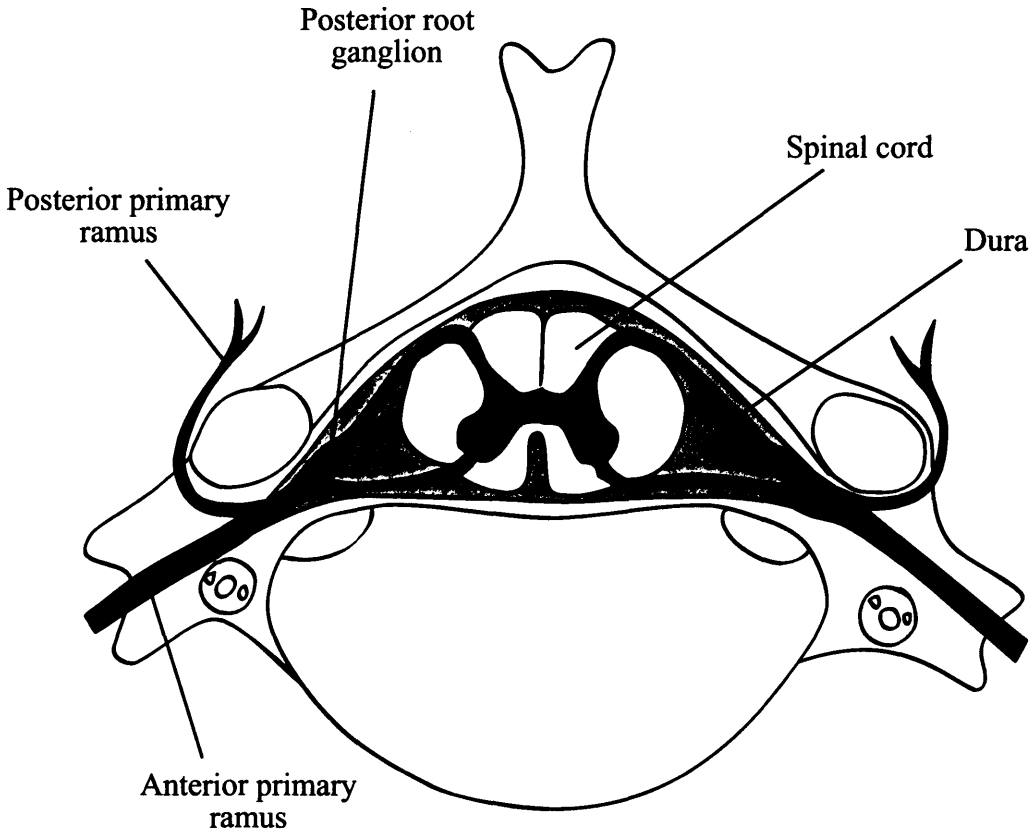


Figure 1.12. The division of the spinal nerve (cervical region) into anterior and posterior primary rami (Pictures taken from Birch, Bonney, Wynn-Parry. Surgical disorders of the peripheral nerves: Churchill Livingstone, 1998 with permission).



Nerve roots

The brachial plexus is formed by nerve roots of lowest cervical segment i.e. C5, C6, C7 and C8 and the first thoracic segment i.e. T1. The anterior primary rami of the lowest cervical segment and the first thoracic segment unite and branch to form the brachial plexus in the lower part of the neck and behind the clavicles. The most proximal muscles are supplied by branches from the rami. The long thoracic nerve is derived via branches from the C5-C7 primary rami and the C5 ramus contributes to the phrenic and dorsal scapular nerves. The axons of the sympathetic preganglionic neurons leave the spinal cord with the ventral roots of the first thoracic to third or fourth lumber spinal nerve. They pass via the white rami communications to the paravertebral sympathetic ganglion chain, where most of them end on cell bodies of the postganglionic neurons. Some of the postganglionic neurons pass to the viscera via the various sympathetic nerves. Others re enter the spinal nerves via the gray rami from the chain ganglia and are distributed to autonomic effectors in the area supplied by the spinal nerves.

Trunks

The three trunks are situated behind the clavicle and sternocleidomastoid in the posterior triangle of the neck and their formation is fairly consistent (Birch *et al.*, 1998). C5 and C7 form the upper trunk whilst the middle trunk is a continuation of C7 and C8 and T1 forms the lower trunk.

Divisions

Each trunk divides into anterior and posterior divisions behind the clavicle. The anterior divisions supply flexor muscles of the upper limb and posterior divisions supply the extensors. The posterior divisions of the upper and middle trunks are larger than the anterior divisions vice versa for the lower trunk and in some 10% of cases there is no posterior division of the lower trunk (Birch *et al.*, 1998; Ferrante, 2004). Usually, there are no terminal nerves arising from the divisions.

Cords

The cords are formed at or just beyond the clavicle. The formation and relationships of the three cords are variable. The lateral cord, formed from the anterior divisions of the upper and middle trunk contains C6-C7 sensory and C5-C7 motor fibres. The three posterior divisions unite to form the posterior cord and contain C5-C7 sensory and C5-C8 motor fibres but do not contain C8 sensory fibres (Ferrante and Wilbourn, 1995).
The medial cord is a direct continuation of the lower trunk and contains C8 and T1 sensory and motor fibres. Nerves arising from the cord innervate different muscles as shown in the Figures (1.11). The branches of the posterior and medial cord are predictable but the branches arising from the lateral cord are variable. For example in about 10% of cases the musculocutaneous nerve arises more distally than usual (Birch *et al.*, 1998) and in 24% of cases, anastomoses between the musculocutaneous and median nerve have been reported (Kawai, 2000).

Terminal nerves (Branches)

The proximal and intermediate muscles of the upper limb are innervated by branches from the trunks and cords, and the muscle of the limb itself by branches from the main terminals nerves, the median, ulnar, musculocutaneous, radial and circumflex nerves Fig 1.11. With the exemption of the median nerve, which arises from the lateral and medial cord, the other terminal branches originate from a single cord. It is unclear at which

point the terminal nerves of the brachial plexus become the peripheral nerves. Narakas defined that point at 3 cm beyond the cord but Wilbourn considers it to be from the point they arise in the axilla (Ferrante, 2004).

1.3.2. Anatomical variations of the brachial plexus

The plexus and the distribution of its nerves vary considerably. Contributions made by the component nerves vary and the origin and method of their formation also varies in some 2% of cases (Birch *et al.*, 1998). Although much has been written about pre and post fixation of the plexus, contributions from C4 and T2 are rare. A significant branch from C4 to C5 or to the upper trunk is 2 to 3% of operated cases. The posterior division of the upper trunk and middle is consistently larger than the anterior division. In some 10% of cases there is no posterior division of the lower trunk. The formation of the cords and branches are also variable. The variations of supply amongst the spinal nerves within the brachial plexus are clinically more important than pre or post fixation (Birch *et al.*, 1998).

1.3.3. Microanatomy of the brachial plexus

The brachial plexus is composed of twice as much connective tissue than neural tissue (Ferrante, 2004). The total number of myelinated nerve fibres in the brachial plexus in the adult is 120,000 and 15000; the eighth cervical nerve is usually the largest, contains about 30,000 myelinated nerve fibres and the fifth and cervical and the first thoracic nerves contain the least number of myelinated fibres, between 15,000 and 20,000 (Birch *et al.*, 1998). The number of sensory fibres in each root also varies: the greatest number is found in seventh cervical nerve, followed by C6, C8, T1 and with C5 having least numbers of fibres (Birch *et al.*, 1998; Ferrante, 2004). At the beginning of the spinal nerves, the motor and sensory fibres are mixed as a result of convergence of ventral and dorsal roots and hence, after mixing of ventral and dorsal roots, it is impossible to determine the topography of the motor and sensory fibres in histological section. The number of fascicles increases from the proximal to distal portion of plexus and the diameter of the fascicles progress inversely (Kawai, 2000).

Table 1.2. Number of myelinated nerve fibres in the brachial plexus (Bonnel, 1984).

	Number of myelinated nerve fibres Average (Range)
Brachial plexus (N=21)	118, 047 (85, 566 – 166214)
C5	16, 472
C6	27, 421
C7	23, 781
C8	30, 626
T1	19, 747
Fibres serving the muscles of scapular girdle	31, 979
Musculocutaneous nerve	5023 (3465 - 9350)
Median nerve	15, 915 (7, 457 - 27, 190)
Ulnar nerve	14, 161 (10, 365 - 22, 690)
Radial nerve	15, 964 (10, 029 – 32, 210)
Axillary nerve	6, 547 (2, 073 - 12, 711)

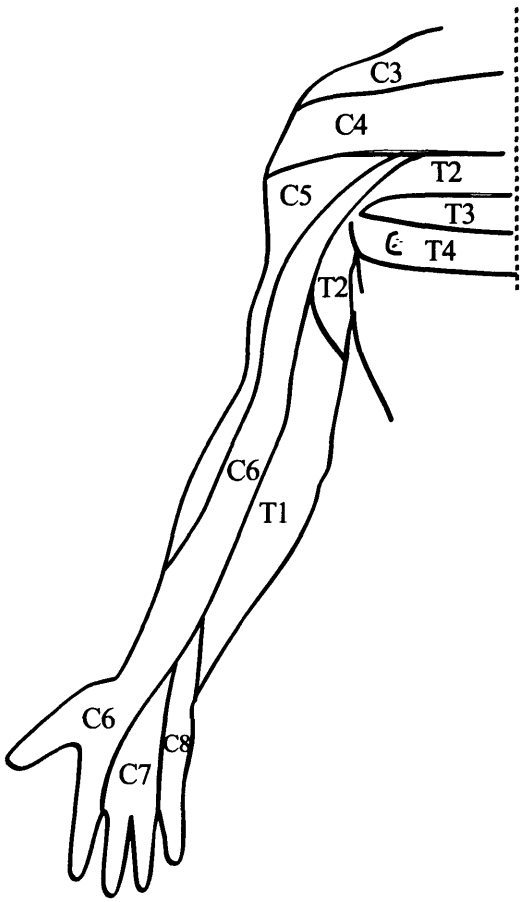
1.3.4. Functional distribution of the brachial plexus

The important anatomical and functional differentiation of the brachial plexus takes place with the division of the trunks into anterior and posterior divisions. From the anterior divisions the lateral and medial cords are formed; from the posterior divisions the posterior cord is formed. The cutaneous distribution of the C5 spinal nerves does not extend distal to the elbow; C6 spinal nerves consistently supply the thumb and index finger; the T1 spinal nerve does not supply the skin of the hand. The C5 spinal nerve usually controls extension, abduction, and lateral rotation of the shoulder; C6 spinal nerve is for abduction, internal rotation and forward flexion of shoulder, pectoralis major (Clavicular head) –elbow flexion and pronation and supination of forearm; C7 spinal nerve is responsible for widespread innervation throughout the limb; C8 spinal nerve is for pectoralis major (sternal fibres), flexor of wrist and long flexor of digits and T1 is for the intrinsic muscles of hand (Birch *et al.*, 1998; Sunderland, 1978).

There is also a segmental pattern of the innervations of the spinal nerves known as myotomes and dermatomes. Myotomes refer to the group of muscles innervated by a single spinal segment and dermatome refers to a cutaneous area in the trunk or limbs supplied by individual nerve roots. The intercostal muscles are, however, the only

muscles which retain a truly segmental arrangement whilst each muscle of the limb is innervated by motoneurons from more than one spinal segment(Sunderland, 1978). In addition, there are a series of overlapping sensory fields and no sharp boundaries between sensory dermatomes (Sunderland, 1978). The nerves and main root supply of muscles can be found in any standard Neurological Text books.

Figure 1.13. Segmental supply of the skin of the neck, upper chest and upper limb. (Pictures taken from Birch, Bonney, Wynn-Parry. Surgical disorders of the peripheral nerves: Churchill Livingstone, 1998 with permission).



1.4. Consequences of nerve injury

There are generally two major consequences following peripheral nerve injury; a biological consequence - degeneration and regeneration and a physiological consequence - reorganisation of the nervous system. Nerves can be damaged in a number of ways by ischaemia, physical agents, trauma, infection, inflammation or the consequence of systemic diseases. Peripheral nerves, including the brachial plexus have a limited ability to react to injury. Trauma to peripheral nerve trunks may result in

variable extent of nerve fibre injury: a focal damage to the peripheral nerve can leads to segmental demyelination or axonal degeneration, which is also known as ''Wallerian degeneration''. Axonal degeneration, is by far the most common process in brachial plexopathies (Wilbourn, 2002) and the fate of the axon is critical for the recovery after injury. In addition to axonal degeneration, there are also changes in the organization of the central nervous system in response to peripheral nerve injury known as ''reorganisation or plasticity ''.

1.4.1. Biological consequence

1.4.1.1. Response to the traumatic injury of a peripheral nerve

A peripheral nerve, regardless of the mechanism of the lesion (e.g., compression, laceration, transaction) responds in a predictable way to injury (Fernandez *et al.*, 1997). Axotomy or crush leads to unavoidable removal of the distal axon segment and associated myelin sheaths (Stoll and Muller, 1999). Swelling, retraction of dendrites, and loss of synapse is accompanied by a decrease in transmitter production and up regulation of the synthesis of neurotrophic protein. Wallerian degeneration is necessary for regeneration to occur as the Schwann cell phenotype changes to support axonal growth (Carlstedt. and Birch., 2004; Maggi *et al.*, 2003; Muller and Stoll, 1998). Transection of the axon induces rapid metabolic and morphologic changes in the affected nerve cell bodies in a relatively predictable fashion (Burnett and Zager, 2004). These complex changes also occur in the segments proximal and distal to the site of injury and distal endings at both the muscle end plates and sensory receptors (Flores *et al.*, 2000).

Neurons that fail to regenerate become atrophic or die by retrograde degeneration and the magnitude of neuronal death depends on the proximity of the lesion. An injury close to the cell body, such as brachial plexus lesion, may result in the death of neurons that would have survived a more distal lesion (Carlstedt. and Birch., 2004; Maggi *et al.*, 2003). There are considerable differences in the reactions of different types of neurons. Primary sensory neurons seem to be more susceptible to injury than motor neurons, with the small, pain-transducing primary sensory neurons appearing to be more vulnerable than larger ones. Gamma motoneurons, which innervate muscle spindles, may die from retrograde cell death, whereas the larger alpha motoneurons usually resist the same type of lesion (Carlstedt. and Birch., 2004). After more proximal nerve injury (root avulsion injury), there is a time dependent deterioration of all motoneurons in the pertinent spinal cord segment (Carlstedt. and Birch., 2004). The interruption of

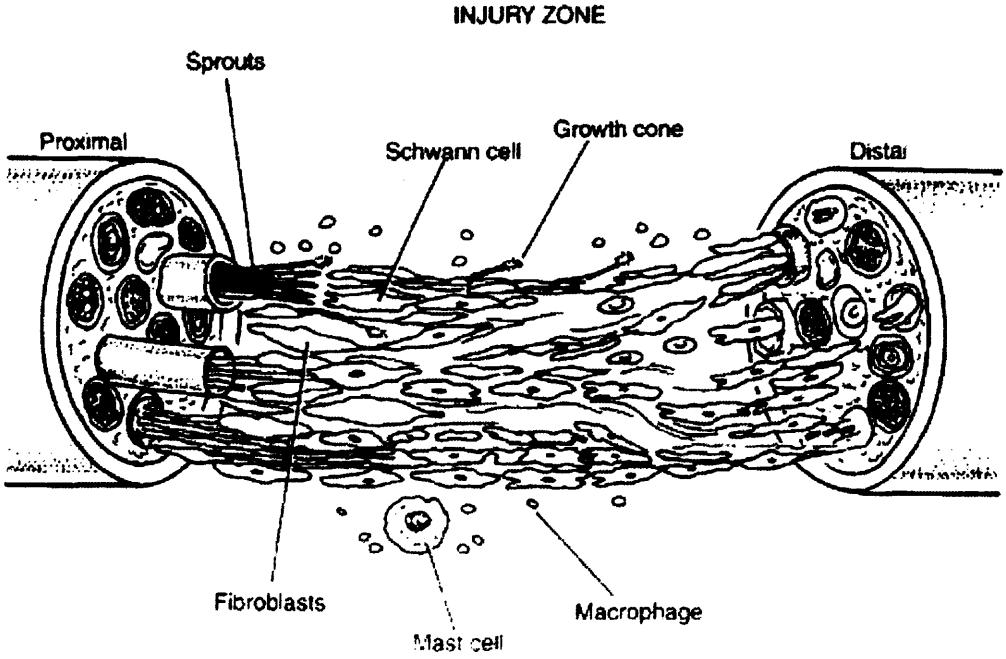
retrograde transport of neurotrophins is of crucial importance and within a few weeks after an avulsion, all spinal cord motor neurons deprived of neurotrophic substances disappear unless reconnection with a peripheral nerve is provided (Carlstedt and Cullheim, 2000).

In severe injuries, nerve regeneration begins only after Wallerian degeneration has run its course, but in mild injuries, the regenerative and repair processes begin almost immediately (Burnett and Zager, 2004). Multiple axonal sprouts emerge at the lesion site or from the node of Ranvier in the proximal axon segment shortly after injury (Ide, 1996). Figure 1.14.

Growth cones at the front end of the sprouts elongate after sending out thin filopodia, which respond environmental signals by retracting or dilating. The response to injury is quite different in the peripheral nervous system compared with central nervous system (Ide, 1996). Tissue support components such as neurotrophic factors and extracellular matrix molecules of the peripheral nervous system support the nerve fibre regrowth, but are not present in the central nervous system (Korsching, 1993). There is therefore a drastic difference in regeneration at the PNS-CNS interface in the spinal nerve roots where growing nerve fibres are impeded (Carlstedt, 1997).

Changes in muscle include shrinkage of cells, thickening of the perimysium and epimysium, and atrophy of the spindle cells. Complete muscle cells atrophy is seen at 2 to 6 weeks, fibrosis between motor fibres develops 12 to 24 months after injury, and fragmentation and disintegration of a denervated muscle can be established at 2 years after injury. Unlike the motor system, recovery of protective sensibility is possible years after nerve injury(Flores *et al.*, 2000). Denervated sensory receptors survive and may make useful functional recoveries after one year and possibly after many years but in cases of severe injury such as third degree nerve injury, recovery is never complete and one of the possible reasons is because of degeneration of the sensory receptors, which are usually modality specific(Burnett and Zager, 2004; Madison *et al.*, 1996; Maggi *et al.*, 2003). The re-innervation of the target is a specific process in motor as well as sensory axonal regeneration(Madison *et al.*, 1999; Muller and Stoll, 1998). It is important to note that axonal regeneration is not synonymous with return of function, for example, a prerequisite for meaningful recovery of motor function after ventral root re-implantation is that motoneurons that re-innervate paralysed muscles are connected adequately to other neurons (Carlstedt and Cullheim, 2000).

Figure 1.14. Schwann cell proliferation in the distal and proximal stumps, with axonal sprouting (Pictures taken from Birch, Bonney, Wynn-Parry. Surgical disorders of the peripheral nerves: Churchill Livingstone, 1998 with permission).



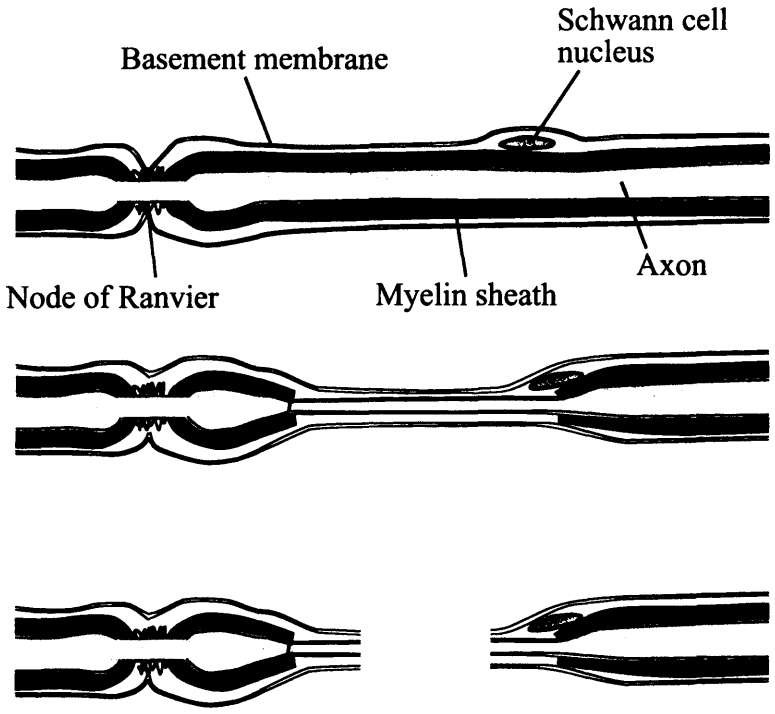
1.4.1.2. Classification of nerve injuries

The timing and success of peripheral nerve repair depends on the extent of injury. Clinically useful injury grading systems have been developed that allow correlation of the microscopic changes occurring after nerve injury with patient symptomatology. Many classifications of peripheral nerve injuries have been suggested, but the most widely used are of Seddon and Sunderland (Seddon, 1954; Sunderland, 1978) with the former more commonly used in literature (Robinson, 2000). Seddon divided nerve injuries into 3 broad categories, and Sunderland uses the more subdivided classification of neurotmesis: their classifications are shown in Table (1.3).

Table 1.3. Classification and degrees of peripheral nerve injuries (Seddon, 1954; Sunderland, 1978)

Sunderland	1st degree	2nd degree	3rd degree	4th degree	5th degree
Seddon	Neuropraxia	Axonotmesis		Neurotmesis	
Electrophysiology	Conduction block	Axonal loss			
Pathology	Segmental demyelination	Loss of axons, with intact supporting structures	Loss of axons, with disrupted endoneurium	Loss of axons, with disrupted endoneurium & perineurium	Loss of axons, with disrupted all supporting structures (discontinuous)
Prognosis	Excellent, recovery is usually complete	Slow recovery; dependent on sprouting and reinnervation	Protracted and recovery may fail because of misdirected axonal sprouts	Unlikely without surgical repair	Impossible without surgical repair

Figure 1.15. Axonotemesis (centre) and neurotmesis at the moment of injury (Pictures taken from Birch, Bonney, Wynn-Parry. Surgical disorders of the peripheral nerves: Churchill Livingstone, 1998 with permission).



Mixed Lesion

It is important to be aware that some nerve injury may not fit in the above classification and there may be a mixture of both axonal loss and conduction block to various degrees which may need careful consideration in evaluation (Robinson, 2000).

1.4.1.3. Regeneration across the transitional region

In mature mammals, neurons cannot negotiate an elongation across the transition region (TR) and grow in and out of the spinal cord. The astrocyte-rich CNS compartment is most effective in preventing regeneration. The lack of appropriate tissue components in CNS, such as nerve growth factors and extracellular matrix molecules together with the presence of growth inhibitory molecules within the CNS are thought to be important in this failure as mentioned above (Korsching, 1993). Thus, regeneration of axons is arrested (Carlstedt, 1985) and after dorsal root lesion, extension of neuronal processes from the spinal cord neurons into the roots does not occur (Carlstedt *et al.*, 1989). The prognosis for the regeneration of motoneurons after injury in the CNS or CNS-PNS junction has been regarded as very unfavourable and in cases of avulsion, they are incapable of regeneration (Cullheim *et al.*, 2002) However, in cat, it was shown that the motoneurons are able to regenerate new axons through the cut lesion in the ventral funiculus of spinal cord, i.e. within the CNS and very proximal to the cell body, to enter the ventral roots (Risling *et al.*, 1983). This unexpected regenerative activity is most probably due to a variety of effects exerted by central scar tissue, the denervated ventral roots and intrinsic properties of motoneurons themselves (Cullheim *et al.*, 1999; Cullheim *et al.*, 2002).

1.4.1.4. Regeneration of the central nervous system

Spinal nerve root avulsion is not merely an injury to the peripheral nerves but a type of spinal cord injury i.e., injury to the central nervous system (Carlstedt *et al.*, 2000; Carlstedt, 1995) and hence the repair process requires axon growth within CNS as well as PNS tissue (Cullheim *et al.*, 1999). The natural ability of the adult central nervous system of higher vertebrates to recover from injury is highly limited and this limitation is most likely due to an inhospitable environment and /or intrinsic incapacity of the neurons to extend their neurites after injury or axotomy (Joosten, 1997). Elements of CNS thought to contribute to the inhibitory microenvironment include myelin and/ or associated molecules and cells inhibitory to axonal growth such as astrocytes, oligodendrocytes, oligodendrocyte precursors and microglia that migrate into the lesion site (Cullheim *et al.*, 1999; Fry, 2001). Absence of tissue support factors and lack of necessary growth promoting molecules and growth factors is also likely to be important as mentioned before (Fry, 2001). There is, however, a potential for regeneration of CNS tissue (Davies *et al.*, 1997; Davies *et al.*, 1999). Following an immediate inflammatory

response, beginning several hours after injury, the distal portion of the severed axon begins to degenerate and the surviving proximal segment may exhibit a regenerative response within six hours of injury such as developing growth cones directing toward the injury (Fry, 2001). But these sprouts are able to extend for only up to 1mm before growth is aborted and the new sprouts are gradually reabsorbed and retracted (Davies *et al.*, 1999; Fry, 2001). Further evidence for the regenerative capacity of CNS is illustrated by David and Aguayo. They demonstrated in animal experiments that after exposing a spinal cord neuron to a transplanted peripheral nerve and by transplanting embryonic cells to the adult central nervous system these regrowing axons failed to elongate when reintroduced into the CNS (Behar *et al.*, 2000; Carlstedt and Cullheim, 2000; Carlstedt, 1995; Fry, 2001; Joosten, 1997). The fate of the neurons in the supraspinal tracts proximal to the spinal axonal injury was studied by Wang *et al* and their data suggested that neurons appear intact after the injury (Wang *et al.*, 2002; Wang *et al.*, 2000).

1.4.2. Physiological consequence: Reorganisation of the nervous system following injury

The peripheral and central nervous system are functionally integrated and there is now universal agreement that the nervous system reorganises in response to nerve injury, playing an important role for functional recovery and hence for management (Chen *et al.*, 2002; Lundborg, 2003).

Reorganisation of the nervous system

It was a traditional view that the adult nervous system is a ''hard wired'' system but now there is considerable evidence that it is consistently modulated in response to activity, behaviour, skill acquisition and deafferentation etc (Chen *et al.*, 2002; Kaas, 2000; Kaas, 2002). Animal and human studies in last two decades have demonstrated that plasticity or reorganisation occurs in the mammalian nervous system in response to central as well as peripheral injuries such as stroke, brachial plexus injury or amputation (Borsook *et al.*, 1998; Chen *et al.*, 2002). A nerve transection represents an acute deafferentation injury with immediate and long term influence on the corresponding representation areas in the brain cortex as well as in adjacent cortical territories (Chen *et al.*, 2002; Merzenich *et al.*, 1983; Wall and Kaas, 1986; Wall *et al.*, 1986). There are different patterns of remodelling according to the nature and extent of nerve injury and

regeneration: for example, the remodelling pattern is different for crush nerve injury and nerve transection followed by surgical repair as the latter is inevitably the presence of misdirection of axons even after repair by microsurgical techniques (Lundborg, 2003). Reorganisation occurs in different parts of the nervous system including the spinal cord, brainstem, thalamus and cortex (Jones, 2000; Tinazzi *et al.*, 1998) and experiments in early blind subjects or partial spinal cord lesions or study of patients whose auditory nerves have been severed suggest that there is also cross-modal plasticity occurring in the brain as well as in long tracts in the spinal cord (Chen *et al.*, 2002; Moller, 2001; Rosso *et al.*, 2003). Florence and Kaas demonstrated that much of the large-scale cortical reorganization that occurs after a major loss of peripheral inputs, reflects the sprouting or expansion of afferents from the remaining forelimb into deprived territories of the spinal cord and brainstem (Devor and Wall, 1978; Devor and Wall, 1981; Florence and Kaas, 1995; Jones, 2000).

It seems that different mechanisms are involved to initiate very fast and more long standing cortical reorganisation (Wall *et al.*, 2002). The fast changes, occurring immediately after deafferentation, are probably based on unmasking of previous, pre-existing but functionally inactive, synaptic connections. Such unmasking of latent connections might explain the rapid expansion of adjacent cortical and sensory cortical territories that follows in deafferentation (Chen *et al.*, 2002; Jones, 2000). Although, unmasking of latent synapses can be due to several mechanisms, it is thought that removal of inhibition of excitatory synapses is due to reduction of GABAergic inhibition (Chen *et al.*, 2002; Lundborg, 2003). Plasticity changes, that occurs over a longer time is likely to involve mechanisms in addition to the unmasking of the synapses. These may include long term potentiation, axonal regeneration and sprouting with alterations in synapse shape, number, size and type (Chen *et al.*, 2002).

While cross-modal plasticity appears to be useful in enhancing the perceptions of compensatory sensory modalities, the functional significance of motor reorganization following peripheral injury remains unclear and some forms of sensory reorganization may even be associated with deleterious consequences like neuropathic (Furue *et al.*, 2004) and phantom pain (Chen *et al.*, 2002). The functional role of reorganisation following peripheral injury is unclear and this phenomenon is being studied by many investigators using methods such as neurophysiology methods (brain mapping and the microneurographic technique of intraneural microstimulation) and imaging techniques(fMRI and PET) (Garraghty and Kaas, 1991; Grusser *et al.*, 2001a; Grusser *et al.*, 2001b; Moore and Schady, 2000; Moore *et al.*, 2000; Tinazzi *et al.*, 2004).

Understanding the mechanisms of plasticity reorganisation is necessary to design appropriate strategies to promote recovery of function (Jain *et al.*, 1998).

1.5. Clinical features of traumatic brachial plexus injury

1.5.1. Incidence and mechanism of injury

The traumatic brachial plexus injury occurs most commonly in young men who are otherwise fit and healthy. The incidence of brachial plexus injury is far more common than is generally appreciated, but only a minority of patients are referred for specialist evaluation and treatment (Goldie and Coates, 1992). The incidence of a closed traction injury of brachial plexus injury in the United Kingdom is between 450 and 500 patients per year (Birch *et al.*, 1998) and the commonest cause of the injury is motorcycle accident (Radek *et al.*, 2000; Terzis *et al.*, 2001). Kim *et al* studied the mechanism of injury involved in 1019 operative brachial plexus injuries and concluded that the brachial plexus can be injured by multiple mechanisms of which stretch/contusion injury is encountered in 49 % of those studied cases (Kim *et al.*, 2004).

Nature and mechanism of injury

The brachial plexus is poorly protected from traction forces due to the loose suspension of the shoulder girdle. In the most severe cases of traction injury, particularly in forequarter dislocation, the nerves as well as the major vessels are at risk of being damaged. If , for instance, the subclavian artery has been seriously injured, which happens in about 15% of these cases, and there is an abolition of pulse in the arm although there might be capillary filling it is mandatory to perform a vascular repair (Birch *et al.*, 1998).

Avulsion of at least one spinal nerve root to the brachial plexus (Fig 4.1) occurs in about 70% of all brachial plexus lesions (Narakas, 1993; Zorub *et al.*, 1974).The lower roots (C8 and T1) to the plexus are more easily avulsed than the upper roots (C5-C7) due to ligamentous support to these nerves at their exit from the foraminae. Strong traction forces that overcome the ligamentous support can cause complete C5 to T1 intra-spinal lesions. Within each injured plexus there are considerable variations - in type of root lesion (Carlstedt, 2000; Carvalho *et al.*, 1997; Privat *et al.*, 1982). There are combinations of total and partial ruptures and avulsions, leaving either the dorsal or ventral root intact. The most frequent pattern is complete avulsion of dorsal and ventral roots (C8 – T1) of the brachial plexus with predominantly the lower roots affected. The combination of intact dorsal and avulsed ventral roots is more common than avulsed

dorsal and intact ventral roots. Most partial root avulsions occur at the upper (C5, C6) nerves of the plexus (Birch *et al.*, 1998; Carlstedt *et al.*, 1995; Carlstedt and Noren, 1995). Rupture of spinal nerves within the intervertebral canal is a less frequently described type of injury (Kline *et al* 1992,Carlstedt and Noren 1995) This type of injury could appear as a most proximal spinal nerve rupture distal to the ganglion (Kline *et al* 1992) where a "classical" nerve graft repair is possible. If, however, the rupture is situated in the proximal part of the intervertebral canal and "pre ganglionic", the injury is, of course, still possible to repair but only with respect to motor recovery (Carlstedt and Noren 1995).This type of injury could be the result of a forceful traction in the upper part of the plexus but is more often, in the case of C8-T1 involvement, a result of a direct impact to the base of the neck (Carlstedt and Noren 1995).

A bilateral brachial plexus lesion is more common in neonates due to birth trauma than in adults. The mechanism behind this type of injury in adults could result from repetitive impact or blast/percussion.

Tension in different roots varies with the position of the arm at the time of trauma. Separation of the neck from the shoulder with the arm hanging down will cause the largest traction force on the upper part of the plexus, i.e. the C5 and C6 spinal nerves and roots. With the arm in a horizontal plane, and particularly with an anterior – posterior directed impact, the middle part of the brachial plexus, particularly C7, is at risk. If the arm is elevated, the lower roots C8, T1 are subjected to the largest traction force.

In a peripheral nerve the epineurium protects nerve fibres from rupture. During progressive stretching, the cross-sectional area within the nerve is reduced causing an increase in intra-fascicular pressure with ischemia due to capillary compression, and initial nerve fibre damage. Further increase in traction will make the epineurium rupture and nerve fibres will then be torn (Haftek, 1970). Studies of stress strain have shown that the maximum load before rupture of a root is about 10 times less than a nerve. A ventral roots are of smaller calibre than dorsal roots and hence more fragile than a dorsal root (Sunderland and Bradley 1961(Sunderland, 1974). C8 and T1 spinal nerves are more vulnerable to avulsion compared with C5, C6 and C7 spinal nerves (Birch *et al.*, 1998).

The weakest point of the root is the junction between the root and spinal cord (Livesey and Fraher, 1992). Avulsion rather than rupture of roots from the spinal cord is therefore the most likely outcome of a severe traction force. Close traction of the

brachial plexus can give rise to either pre-ganglionic injury i.e. intra-dural rupture; avulsion or postganglionic injury i.e. ruptures of the spinal nerves. Fifteen percent of such cases, have lesions at two levels (Birch *et al.*, 1998). Rootlets are not surrounded by connective tissue and hence are unprotected and easily torn by stretching. The true avulsion is in fact, injury to the spinal cord in the central nervous system (Carlstedt *et al.*, 2000), Involvement of the central nervous system represents the most serious complication of traction injury and a Brown-Séquard syndrome of varying degree is found in about 10 % of complete avulsion injuries (Birch *et al.*, 1998). It is unlikely that this occurs as a result of a direct mechanical effect upon the spinal cord, for example, adjoining pieces of the spinal cord being torn away with accompanying roots in severe traction injuries. Such speculation is anecdotal in the surgical community and there is no direct evidence provided from examination of the intact nature of the spinal cord to substantiate this.

The tear occurs in the transitional region of the peripheral and central nervous system (Berthold and Carlstedt 1977) which makes this a lesion of the central rather than peripheral nervous system. There is secondary degeneration along the proximal axons of motoneurons and the distal sensory nerve fibres in the spinal cord following the trauma. Symptoms associated with long fibre tracts are could be due to result from ischemia caused by the circulation being compromised.

Although, the exact events behind root avulsion are not completely understood, two mechanisms peripheral and central have been described. The peripheral mechanism is a lateral or peripheral traction force onto the root and spinal nerve, which when forceful enough, displaces the ganglion from the interveterbral foramen (Fig 5a) (Mansat 1977, Mansat *et al* 1979) consequently the roots are severed from the spinal cord. The roots and the ganglion could after such a traction be found in between the scaleni muscles or even further distally, underneath the clavicle. In the central mechanism the roots are detached from the spinal cord but the ganglion and the roots have not been displaced out of the spinal canal or the foramen (Fig 4). This paradoxical situation is thought to depend on an axial rather than a lateral force occurring during a shift in the spinal cord from an excessive lateral flexion of the spinal cord (Sunderland 1974). By the excessive lateral flexion of the neck the spinal cord pulls in cranial direction away from the roots which are anchored at the intervertebral foraminae (Fig 4,5b). This type of root avulsion occurs in particular when there has been an impact to the cervical spine, sometimes with vertebral fractures, rather than a trauma to the shoulder. A mixture of a peripheral and

central mechanism of root avulsion can sometimes be seen when exposing the spinal canal This type of injury is probably most common in obstetrical brachial plexus injuries when shoulder dystocia necessitates excessive lateral flexion of the neck. At extra-spinal exploration only, in the posterior triangle of the neck, there is a false impression of an uninjured plexus with spinal nerve in situ up to the foraminae. A certain diagnosis of a severe intra-spinal lesion is difficult to reach in this situation.

1.5.2. Clinical presentations

Most patients with traumatic brachial plexus injuries usually have associated traumatic injuries such as fractures, head injury and chest injury etc(Kawai, 2000; Midha, 1997). Meticulous history taking and clinical examination is crucial in order to assess the extent and level of injuries which have implications for the clinical management plan(Birch *et al.*, 1998).Initial and subsequent symptoms and circumstances surrounding the onset, especially the violence of the injury and the mode of application of the force to the damaged limb are of particular importance (Birch *et al.*, 1998; Ferrante, 2004). Usually both ventral and dorsal roots are involved in brachial plexus injury, and the patient is subjected to paralysis and sensory dysfunction with numbness in the limb combined with extreme, almost unbearable, intractable pain (Carlstedt *et al.*, 2000; Wynn Parry, 1980). In supraclavicular lesions, the pattern of motor and sensory loss is segmental (myotomal and dermatomal). These may also be associated with Horner's syndrome and dysautonomic features on the affected side and features of involvement of phrenic, dorsal scapular and long thoracic nerve palsy.

The description of pain in a proximal brachial plexus injury is characteristic, a constant burning and crushing pain which may be associated with intense shooting pain, which can allow to give a precise diagnosis (Birch *et al.*, 1998). Another important physical sign which is a significant indication of the postganglionic rupture is ''Tinel's sign'' (Birch *et al.*, 1998).

1.5.3. Classification of traumatic brachial plexus injury

Generally, brachial plexus injury can be classified according to the region involved; supraclavicular, retroclavicular and infraclavicular lesions. The supraclavicular lesion is the commonest, usually most severe and associated with a high incidence of rupture or preganglionic injury to the spinal nerves with vascular lesion. Five percent of the complete lesion is associated with damage in the spinal cord (Birch *et al.*, 1998; Ferrante, 2004; Midha, 1997). This anatomical classification is simple but there are

distinct groups amongst supraclavicular lesion and the severity may differ and hence the prognosis. This has been acknowledged and divided according to the nature of brachial plexus injury as described by Birch *et al* as follows(Birch *et al.*, 1998):

A. The upper lesion: rupture or avulsion of C5 and C6 (C7) with intact (C7) C8 and T1. This is the most favourable lesion because there is useful hand function.
B. The lower lesion: Intact C5 and C6 (C7) with rupture or avulsion of C8 and T1. There are opportunities for useful palliation but the prognosis is generally poor except that the repair is performed within days of injury.
C. The middle lesion: Recovery of C5 (C6) and T1 (C8), with rupture or avulsion (C6) C7 (C8). This pattern is less common in adults and the prognosis generally into one or other of above categories.
D. The complete lesion: In the case of rupture, modest function can be expected from the graft and in case of total avulsion the only real prospect of regaining function lies in re-implantation because nerve transfer is only mitigation.

1.6. Investigation of traction brachial plexus injury

Although the history and physical examination remains the cornerstone for the evaluation for the diagnosis of traction brachial plexus injury, the assessment of the injury is supplemented by investigations such as physiological testing, electrodiagnostic investigations and imaging.

1.6.1. Axonal reflex testing

Histamine and cold vasodilatation tests

Bonney developed the concept of pre- and postganglionic injury, distinguishing between injuries to the spinal cord and those to peripheral nerves. He described the persistence of an axonal reflex in preganglionic injuries of the brachial plexus after injection of histamine and preservation of the cold vasodilatation response in preganglionic injury (Bonney, 1954).

1.6.2. Neurophysiological investigation

The brachial plexus is more difficult to evaluate electrodiagnostically than most other parts of the peripheral nervous system because of the complex nature of its anatomy (Burge, 1997). Almost all of the major components of the brachial plexus can be assessed by nerve conduction studies and needle electromyography examination to determine pathophysiology, location and severity (Wilbourn, 2002). Neurophysiological

investigations, particularly needle electromyography, however, cannot be applied sooner than 2 weeks after the injury (Burge, 1997), and unfortunately, this undermines its usefulness in the treatment of acute brachial plexus injury because prompt repair is crucial for the best outcome. Intra operative neurophysiological study is also useful to determine the level of lesion and assess the viability of the nerve (Landi *et al.*, 1980; Oberle *et al.*, 1997a; Oberle *et al.*, 1997b). Preservation of sensory nerve action potential implies that the nature of the lesion is preganglionic and the presence of sensory evoked potential implies continuity of the posterior roots to the spinal cord (Deletis *et al.*, 1995). Combination of sensory evoked potential (SEP) and sensory nerve action potential (SNAP) findings can suggest a location for the lesion (preganglionic, postganglionic or combining pre-and postganglionic elements) which has been found to be accurate in 10 out of 16 operated cases(Jones *et al.*, 1981). It has been documented that there is a clear relationship between the state of the root as documented by intradural root inspection and the results from intraoperative recording of evoked potentials(Oberle *et al.*, 2002). Intraoperative trans-cranial or trans-spinal motor evoked potential (MEP) recording is particularly useful in assessing the functional status of anterior motor roots and motor fibres in exposed spinal nerves (Oberle *et al.*, 2002; Turkof *et al.*, 1997).

1.6.3. Imaging

Plain radiograph are useful for the diagnosis of bone injury as well as to assess the extent of injury (Birch *et al.*, 1998; Ferrante, 2004; Spinner and Kline, 2000). Elevation of the ipsilateral diaphragm confirms phrenic nerve palsy and is an indication of the level of injury of C5 and C6.

Myelogram, CTM (CT-Myelogram) and MRI (magnetic resonant imaging) are widely used for the assessment of traction brachial plexus injuries. Murphy and Kirklin were the first who used cervical myelography for investigation of traction brachial plexus injuries (Murphey and Kirklin, 1973). Myelograms demonstrating pseudomeningocele, poor root sleeve filling, cord oedema, or cord atrophy correlate strongly with root avulsion(Spinner and Kline, 2000). Myelogram, however, particularly, oil-soluble media was found underestimate the severity of injury and now it is widely replaced by using water-soluble contrast material combined with computed tomography (CT) scanning, known as CT- myelography (Birch *et al.*, 1998; Leffert, 1988), which claims to be more sensitive than myelography (Marshall and De Silva, 1986).

MRI performed early after traction injury to the brachial plexus, provides useful additional information towards establishing the level of the lesion. There were no false positives but MRI underestimated the number of individual roots avulsed. Sensitivity was 81% and MRI also provides information about injury to the plexus outside the spinal canal (Bilbey *et al.*, 1994; Hems *et al.*, 1999). MRI becomes the modality of choice for more distal brachial plexus imaging and valuable tools for detecting bleeding within the spinal canal and/or displacement of the spinal cord. Although MRI is increasingly used to assess brachial plexus injury, CT-myelography is more sensitive for the detection of avulsion injury: The accuracy of the preoperative CT myelography-based diagnosis in relation to the intraoperative findings was 85%. On the other hand, MRI demonstrated an accuracy of only 52% (Carvalho *et al.*, 1997). Magnetic resonance myelography is a newer technique, which could become a useful adjunct for assessing proximal brachial plexus lesions (Ferrante, 2004).

12% of patients who had traumatic brachial plexus injuries also had associated vascular injuries (Slooff, 2001) and conventional angiography is frequently indicated but it has been widely replaced by Magnetic resonant angiography (MRA).

1.7. Treatment of Traction brachial plexus injury

Early exploration is a priority apart from the management of associated life threatening injuries for a number of reasons: the technicality of surgical repair is easier; intra operative assessment of the status of the nerves involved is feasible; more options for the nerve repair are available and hence it is possible to achieve a better outcome (Birch *et al.*, 1998). The more common current practice of repairing spinal cord root avulsion injuries is to transfer an intact neighbouring nerve to the distal stump of the damaged nerve in order to restore some motor and sensory function. The intercostal and accessory nerves are commonly used for this purpose (Berman *et al.*, 1998). .

1.7.1. Strategies of repair

Birch *et al* summarised the strategies of repair as follows: (Birch *et al.*, 1998)

Partial Lesions

Ruptures of C5 and C6 (C7); intact (C7) C8 and T1

Accessory to suprascapular transfer

Standard graft for ruptures

Preganglionic C5 and C6; intact C7, C8 and T1

Reinnervation of nerve to serratus anterior necessary in 30% of cases

Accessory to suprascapular transfer

Intercostals T4 and T5 to circumflex transfer

Ulnar to biceps transfer (Oberlin)

Depending on sensory loss, and the presence of C7 fibres in the lateral cord, transfer the medial cutaneous nerve of forearm and/ or superficial divisions of T3 and T6 to the lateral root of median nerve

Preganglionic C5 and C6 and C7; intact C8 and T1

Reinnervation of nerve to serratus anterior usual

Accessory to suprascapular transfer

Ulnar to biceps transfer (Oberlin), or T3 and T4 to musculocutaneous

Superficial divisions T5 and T6, and/ or medial cutaneous of forearm to the lateral root of median nerve

If ulnar to biceps is used, T3 and T4 are available for the lateral pectoral and thoracodorsal nerves

Early flexor to extensor tendon transfer (using flexor digitorum superficialis and palmaris longus) required in about 50% of cases

Mixed ruptures and Preganglionic C5, C6, C7 and C8; intact T1

Combined grafts and transfers to reinnervate the limb

The aim in this group is to restore all major joint functions

Complete lesions

Ruptures C5 (C6, C7, C8); preganglionic (C6, C7, C8) T1

Accessory to suprascapular nerve transfer:

If three healthy nerve roots available: repair whole plexus

If two healthy nerve roots available: repair upper and middle trunks, and T3, T4, T5 and T6 for medial cord

If one healthy nerve root available: repair lateral cord, T3, T4, T5 and T6 for median cord

Alternatively, transfer accessory and/ or dorsal scapular nerve to ventral roots of avulsed spinal nerves and supraclavicular nerves to the nerve just distal to the dorsal root ganglion

Total Preganglionic: phrenic nerve working

Nerve transfers for the serratus anterior; suprascapular nerve; elbow flexion; median nerve sensation

Total Preganglionic: phrenic nerve palsy

Reinnervate serratus anterior (part of dorsal scapular nerve)

Accessory to musculocutaneous nerve

Intercostals, superficial divisions only, to median nerve

The aims of the treatment in the complete avulsion group are much narrower: stability of shoulder girdle, elbow flexion and relieve of pain

A surgical re-implantation technique for restoration of function after ventral root avulsion injuries in man has already been introduced and this technique is reserved in patients with severe brachial plexus injury and again early reimplantation after the trauma appeared necessary for a good outcome (Carlstedt *et al.*, 2000; Carlstedt *et al.*, 1995)

1.7.2. Reconstructive surgery and other palliative procedures

Functional recovery of the injured limb can be augmented by various measures such as tendon transfer. Artherodesis and amputation are also used in particular cases. It is also important to treat pain which could be intractable in brachial plexus injury. Nearly all patients with preganglionic injury of a spinal nerve experience pain and there is good evidence that re-innervation of the limb improve the pain (Birch, 1992). However, pain relief after surgery is unpredictable and may need to be treated by other measures such as prescription of a variety of medications, manipulation on of the central nervous system either surgically or chemically (Birch, 1992).

Lastly, but most importantly, multidimensional approaches to rehabilitation of the patients, which allow to return of a normal working life is crucial in treating the patients with brachial plexus injury.

Chapter II: Hypothesis and Objectives of Study

There are changes in motor, sensory and autonomic function in patients with severe brachial plexus injury. These changes, including regeneration of long fibre tracts and / or segmental connections, reflect structural and functional plasticity which can be assessed by clinical and/ or neurophysiological investigations. It is hypothesized that the functional changes generated by lesions and different management strategies, are reflected as regeneration in the central and peripheral nervous systems and can be investigated in distinct clinical models. Thus, after developing and investigating the hypothesis-driven models (which are described in detail in Chapter III), functional recovery of the spinal nerve root injury has been evaluated. The findings from each model may enable the design of new, interventional strategies for repair of the brachial plexus and spinal cord.

Aim of Thesis

1. To evaluate the outcome of functional recovery after brachial plexus injury repaired by different surgical *strategies.*
2. To evaluate the long term outcome of functional recovery in patients repaired by spinal cord re-implantation of avulsed roots.
3. To evaluate motor and sensory clinical phenomena such as synkinesia, ''breathing arm'' and ''referred sensation'' after repair of the brachial plexus.
4. To evaluate the effect of surgical repair on pain.

Chapter III: Materials and Methods

Inclusion and exclusion criteria of patients recruited for these studies are described in this chapter. The number of patients studied for each clinical model is cited in the relevant chapter. The methods employed in this study are also detailed in this chapter.

3.1. Patients

Included patients have spinal root avulsion, which was confirmed at surgery by direct observation of the exposed brachial plexus and electrophysiological studies. In addition, they had diagnostic records from computerised topographical (CT)-myelography, per-operative electrophysiology, and inspection of the spinal cord (if applicable). Patients were excluded if they had associated, direct spinal cord or brain injury, injury to proximal major blood vessels, or double-level lesions. All patients underwent surgery at the Royal National Orthopaedic Hospital, Stanmore. They were assessed clinically, pre-operatively and at different intervals post-operatively. Neurophysiological studies were performed at the Hammersmith Hospital. Ethical permission for all of these studies was obtained from the local research ethical committees at the Royal National Orthopaedic, Hammersmith and St. Mary's Hospitals, and informed consent was given by patients.

Clinical models have been developed (see below) to elucidate clinically-important mechanisms of structural and functional plasticity, and to provide evidence of spinal cord regeneration in the following groups:

1. Patients with spinal cord root avulsion and ventral and/or dorsal root re-implantation.
2. Patients with spinal cord root avulsion without re-implantation to spinal cord, but with nerve transfer.
3. Patients with spinal cord root avulsion but without repair (late referrals/"historical" cases).
4. Patients with injuries distal to the dorsal root ganglion, and repaired by conventional grafts

Referral

3.2. Clinical Models:

1. Motoneurone regeneration and connectivity in spinal cord.
2. Co-contractions in limb muscles and "the breathing arm".
3. Sensory recovery.

4. Referred sensations.
5. Pain.

Clinical Examination and Neurophysiological Testing

3.3.1. Motor function

All patients underwent a detailed neurological examination. Motor power in the upper limb was assessed using the grading recommended by the Medical Research Council, Table 3.1 (Seddon, 1954).

Table 3.1. Medical Research Council (MRC) grading for the assessment of motor power

0 = Complete paralysis

1 = Flicker of contraction

2 = Contraction only gravity eliminated

3 = Contraction against gravity only

4 = Contraction against gravity and some resistance

5 = Contraction against powerful resistance. Normal power

The source of recovery was analysed according to the nature and site of the lesions and methods of surgical repair. Muscles can be innervated by more than one spinal nerve root but not all the spinal nerves supplying these may be damaged. Muscles with multiple nerve root supplies were not included in the study in order to avoid the risk of over optimistic calculation of muscle motor recovery due to remaining/residual intact nerves which may have been spared injury. For example, the power of the sternal head of the pectoralis major was not included in the study if the lower plexus was intact. Those muscles retaining some strength before surgical repair were also excluded. For example, the power of the serratus anterior was often preserved in a rupture of the C5 nerve and hence excluded from the calculation for the recovery of C5, C6 and upper trunk rupture. In some patients, intercostal nerve transfers were carried out to relieve pain and were omitted from evaluation of motor recovery. The results can be evaluated only after sufficient time has elapsed because re-innervation is always delayed after nerve grafting. Two to three years is generally thought to be required for any clinical recovery to be detected but this depends upon the type (avulsion, rupture etc.) and location of the lesion (roots, trunks, cord, and terminal branches)(Alnot, 1995).

Functional recovery of the shoulder and elbow was also assessed using Narakas's functional scoring system (Table 3.2). This scoring system allows comparison of results between different types of repair. It can be used to evaluate global functional recovery, especially of the shoulder and elbow, rather than individual muscles, although functional recovery may come from more than one type of repair. Since most of the patient in this study had more than one type of repair, comparison of these scores is possible only for limited numbers of patients who regained functional recovery from either re-implantation with other repairs or other surgical repairs without re-implantation.

Table 3.2. Narakas' score chart (Birch et al., 1998).

Function	0	1	2	3	4	5
Shoulder: Max. 13 points						
Abduction and/or forward flexion (max. 5 points)	Flail	0-30° stable	30°-60°	60°-90°	90°-120°	>120°
External rotation (max. 4 points)	0	0-10°	10°-30°	30°-60°	60°	
Thoracobrachial grasp (max. 2 points)	0	Can hold a file against chest	Can hold a bag weighing 1 kg or more against chest			
Posterior projection (max. 2 points)	Nil	Wrist can be brought to lateral aspect of hip	Wrist behind plane of glutei or better			
Elbow: max. 9 points						
Flexion (5 points)	0	Hand to pocket or belt	To 90° against gravity	To 90° with 1 kg in hand	To 90° or more with 3 kg	Flex 90° or more with 3 kg
Extension (4 points)	Not possible	Full extension	Extends with 1 kg	Extends with 3 kg	Better than 3 kg	

3.3.1.1. Co-contraction and the "breathing arm"

After the repair of spinal nerve root injury, co-contraction of a group of limb muscles (agonist and antagonist) and rhythmic contraction of a limb muscle can occur in synchrony with respiration: the "breathing arm". This motor phenomenon was examined clinically when possible and recorded by EMG (see below).

3.3.2. Electromyography (EMG) examination

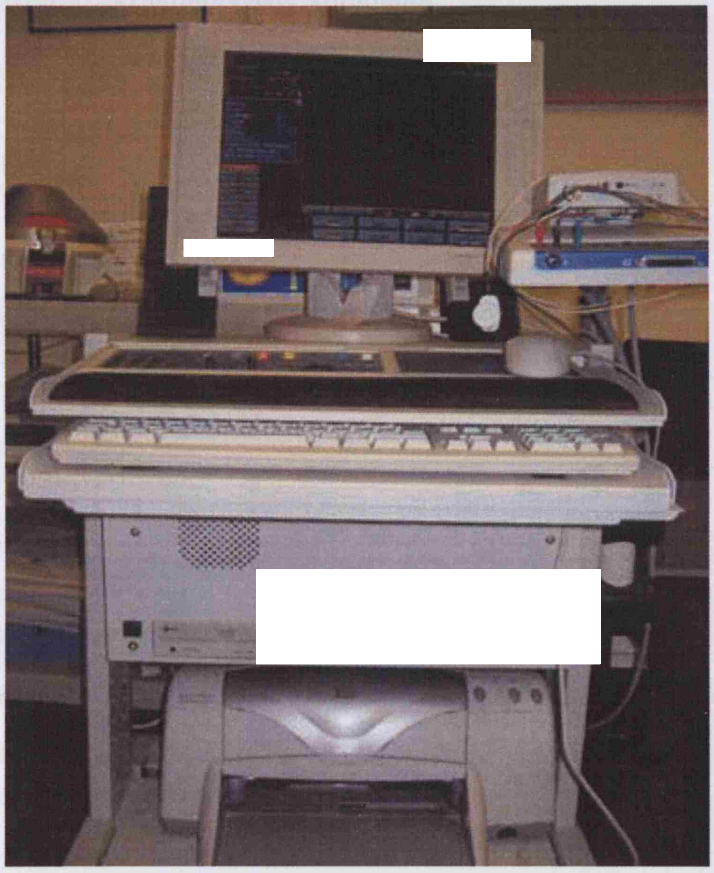
Concentric needle (TECA disposable needle; Oxford Instruments Medical, Surrey, UK) EMG examination was performed with a new version of the Keypoint® work station (Medtronic Functional Diagnostic A/S, Skovlunde, Denmark). Various muscles were sampled using conventional electromyographic methods including insertional and spontaneous activities, motor unit action potentials (MUPs), and recruitment. In addition, motor unit activity was examined in relation to respiration and cough. Multi-channel, simultaneous, surface EMG recordings of the pectorals, deltoid, biceps and triceps muscles were made in order to determine the presence of co-contractions of limb muscles with voluntary movements and respiration. HUSH™ Alligator Clip Cables (Medtronic, Dentec, Skovlunde, Denmark) and TECA NCS 2000 pre-gelled, self adhesive disposable electrodes (Oxford Instruments Medical, Surrey, UK) were used for surface recording.

Table 3.3. Machine settings for EMG examination.

Parameter	Resting	Motor Unit	Recruitment	Co-contraction/ Breathing arm
Sensitivity	50 μV/division	200μ V/division	1 mV/ division	0.5 to 1 mV/ division
Time base	10 ms/ division	10 ms/ division	10 ms/ division	150 ms to 2 seconds /division
LFF	10 Hz	10 Hz	10 Hz	10 Hz
HFF	32 KHz	32 KHz	32 KHz	32 KHz

LFF; Low frequency filter, HFF; High frequency filter

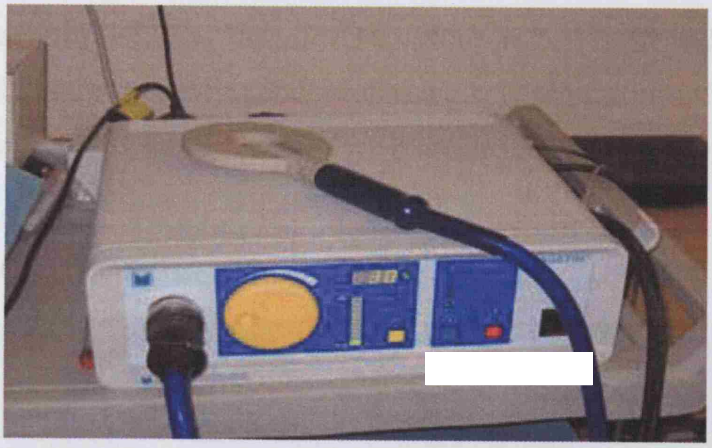
Figure 3.1. Keypoint® work station.



3.3.3. Magnetic stimulation

Single pulse, Transcranial Magnetic Stimulation was performed using a Magstim®200 Monophasic stimulator (Novametrix Medical Systems Ltd., Whitland, UK). The output was connected to a new version of the Keypoint® work station (Medtronic Functional Diagnostic A/S, Skovlunde, Denmark) to record responses. A stimulating circular coil (High power 90 mm coil) was placed over the head of the patient corresponding to the region of the motor cortex on both sides (the centre of the coil placed centrally on the vertex). To record the best responses from the muscles, the coil was positioned with Side A up over the left side of the motor cortex (to record the right side of the body) and conversely Side B was up over the right side of the motor cortex (to record the response from the left side of the body). The maximum, consistent, motor evoked response was recorded from upper limb muscles. (pectorals, deltoid, biceps and triceps). HUSH™ Alligator Clip Cables (Medtronic, Dentec, Skovlunde, Denmark) and TECA NCS 2000 pre-gelled, self adhesive disposable electrodes (Oxford Instruments Medical, Surrey, UK) were used for surface recording. Facilitation was used whenever possible. Both injured side and the contra-lateral (normal) side were studied.

Figure 3.2. Magstim®200 Monophasic Stimulator.



3.3.4. Sensory examination and tests

The following sensory examinations and tests were performed with the patient's eyes covered or closed:

Touch

This sensation was examined by touching the skin with a cotton wool and a dedicated disposable pin. The sites tested were chosen using dermatomal maps based on a Medical Research Council memorandum(Seddon, 1954) (MedicalResearchCouncil, 1976) and these were recorded as either abnormal or normal.

Joint position sensation

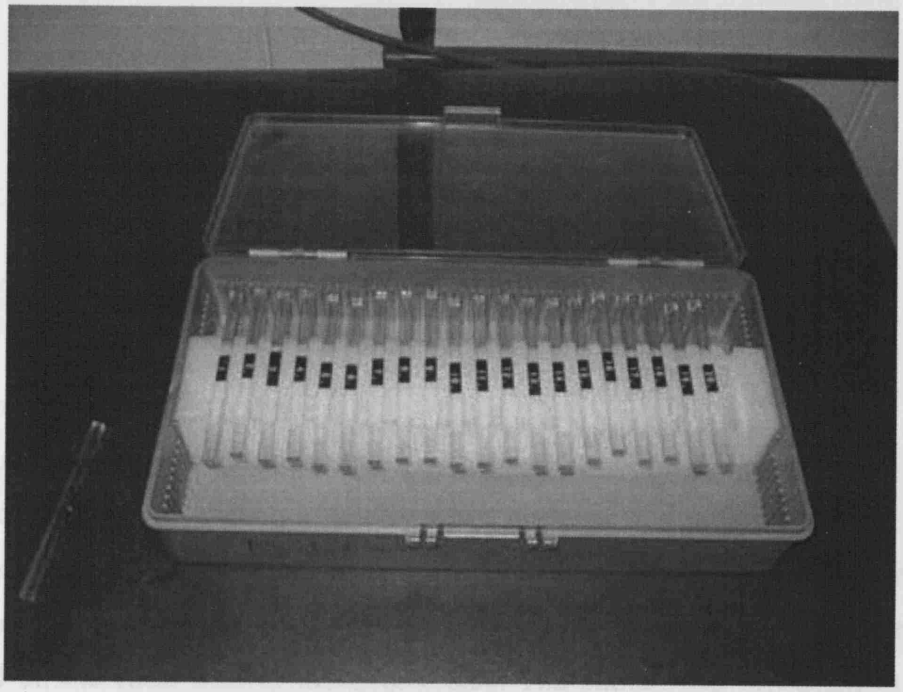
Joint position sensation was tested at the fingers, wrist, elbow and shoulder joints. The examiner moved the patients' joints and a random sequence of direction of small or large movements tested. Patients were asked to identify the direction of movements. Throughout the examination procedure, the examiner attempted to prevent the patients from guessing. Joint sensation was classed as abnormal if the patient failed to give the correct direction or could detect only crude and not fine movements.

Quantitative light touch thresholds

Light touch thresholds were determined using Semmes-Weinstein Monofilaments (made by A. Ainsworth, University College of London, UK)(Figure 3.3). The monofilament was placed on the skin with a pressure just adequate to bend it. The

monofilaments were numbered 1 to 20 and the lowest monofilament number detected reliably (three or more out of five trials) recorded. Value greater than number 3 monofilament (0.0479g) was considered "abnormal". Theoretical values (g), corresponding approximately to monofilament numbers 5, 10, 15 and 20, are 0.132, 1.66, 20.9 and 263.0 respectively. The relationship between the monofilament and log 10 force is linear thus enabling a statistical analysis(Quraishi et al., 2004).

Figure 3.3. Semmes-Weinstein Monofilament equipment.



Quantitative vibration perception thresholds

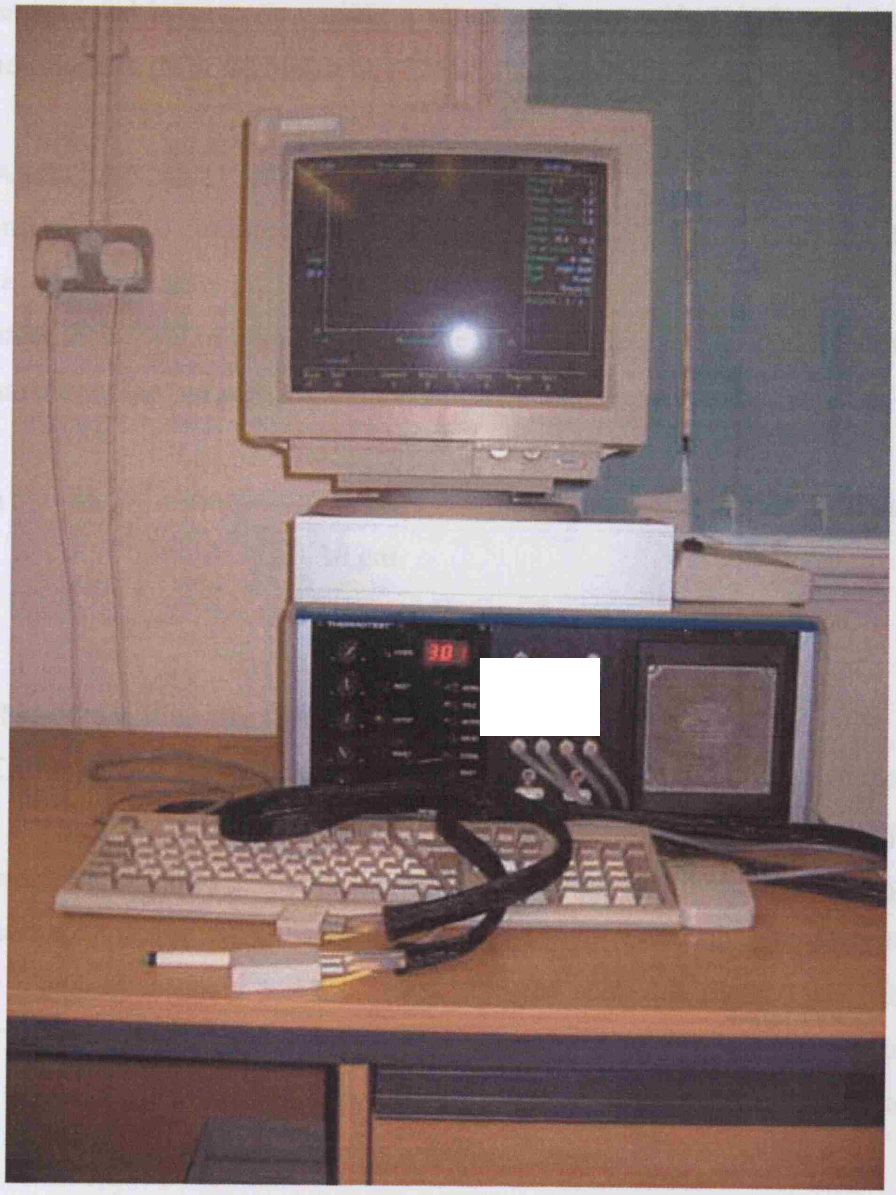
Vibration perception thresholds were measured using a biothesiometer (Biomedical instrument Co., Newbery, OH, USA) (Figure 3.4). The stimulating probe was placed at the distal interphalangeal joint of the appropriate finger, or at a bony prominence in more proximal joints. The patient was asked to reply "yes" as soon as the vibration was perceived during an increasing ramp (perception threshold) and "yes" again as soon as the vibration disappeared with decreasing ramp (disappearance threshold). Three ascending and three descending trials were carried out, and mean values obtained. The vibration threshold was determined by the method of limits and expressed on an arbitrary scale in volts where any value >10V was considered "abnormal ".

Figure 3.4. Biothesiometer.

Quantitative thermal threshold:

Assessment of thermal thresholds were carried out in a silent room with an ambient temperature of 20-23°C using a modified Marstock method with a Somedic thermo-stimulator (Stockholm, Sweden ;Figure 3.5). The thermode was placed according to the dermatomal distribution on the skin of the injured limb, at the border zone area, neck, face and on the chest wall of the injured side. The patient was instructed to press a button as soon as a warm or cool sensation was perceived. The baseline temperature was 30°C with a rate of change of 1°C per minute. The range for cooling and warming was 10 - 50°C. The first trial was carried out on the contralateral side. Detection thresholds for cool (CDT) and warm (WDT) were determined by the method of limits and recorded as a mean of four trials. Values >2SD above the mean were considered "abnormal" (2.6°C for cool sensation and 3.9°C for warm sensation).

Figure 3.5. Somedic Thermo-stimulator.



3.3.5. Referred sensation

Recovery of sensation, after brachial plexus injury, albeit abnormal in modality and experienced at remote sites, is termed "referred sensation". General descriptions of referred sensations were recorded and could be provoked by mechanical, thermal and electrical stimuli. The timings of the phenomena were recorded and documented where possible. The equipments described above were used also to record mechanical and thermal sensations. For an electrical stimulus, a TENS machine (Model TP 120Z, RDG MEDICAL, Surrey, UK) with a pulse width of 200 microseconds and a burst mode of maximum 9 pulses per burst was used and an electrical stimulus of 2 bursts per second applied.

3.3.6. Pain evaluation

Pain was assessed by interview using a visual analogue scale (VAS) and the McGill Pain Questionnaire (MPQ) ;(Melzack, 1975).

Visual Analogue Scale (VAS)

VAS consists of a 10 cm line anchored at two extremes of pain: no pain and the worse pain one could possibly imagine. Patients are asked to make a mark on the line representing their level of perceived pain intensity, and the scale is scored by measuring the distance from the 'no pain' end to the patient's mark.

No Pain |——————————————————————————| Worse pain possible

10 cm

McGill Pain Questionnaire (MPQ)

The McGill Pain Questionnaire (MPQ) was employed to assess different components of reported pain. Patients were asked to indicate the location of their current pain and choose words to describe it from a list of 78 adjectives. The three major categories of pain descriptors in the MPQ were sensory, affective and evaluative (Appendix 1). Separate scores for sensory and total were obtained using the method of "Number of Words Chosen (NWC)". The NWC was obtained by counting the number of words selected by the respondent. Separate scores for sensory and total pain were calculated based on the "rank values" of the words within each category.

3.3.7. Sweating evaluation

Sweating was measured in the palm of the hand using an evaporimeter (Servomed, Stockholm, Sweden; Figure 3.6). The evaporimeter has two sensors which measure the relative humidity in an open cylinder at different distances from the skin surface. Signals derived from these transducers are computed to provide a partial pressure of the water vapour gradient, and the evaporation rate in $g/m^2/h$. Values < 50% of those in the contralateral palm were considered to be "abnormal".

Figure 3.6. Evaporimeter.

3.4. Statistical Analyses

Statistical analyses were made using GraphPad Prism software version 3.0, 1999 (GraphPad Software, Inc, San Diego, CA, USA). Data are presented as mean ± SEM (standard error of the mean) if not otherwise stated. If the samples were in 3 or more groups, group characteristic were compared using the Kruskal-Wallis statistic. Samples of only two groups were compared using the Mann-Whitney U test.

For pain studies, the association between two variables such as severity of lesion and severity of pain were measured using correlation statistical methods (Spearman r and linear regression) statistical methods. The level of statistical significance was set at *P*-values <0.05.

Chapter IV: Recovery of motor function after surgical repair of brachial plexus injury

4.1. Summary

Nerve root avulsion from the spinal cord occurs frequently in brachial plexus traction injuries. Common current surgical practice for treating avulsion injuries is to transfer an intact neighbouring nerve to the avulsed nerve, in order to restore some motor and sensory function. Recently, the surgical strategy of re-implanting avulsed spinal roots or nerve grafts to the spinal cord has been applied in patients with severe brachial plexus injury.

Fifty one patients who sustained total brachial plexus injury with avulsion of spinal nerve roots were repaired by various surgical procedures and studied clinically and neurophysiologically. The recovery was analysed taking into consideration according to the nature and site of the lesions and methods of surgical repair. The efficacy of intra spinal repair (re-implantation) of a complete brachial plexus avulsion injury was comparable to that achieved from reconstruction of a less severe, brachial plexus injury of upper spinal nerve ruptures. Spontaneous contractions of limb muscles in synchrony with respiration, the "breathing arm", were noted in twenty six out of thirty seven patients. In three patients, the source of the breathing arm followed re-implantation and provided evidence of regeneration from the spinal cord to the periphery. We conclude that, after repair of the spinal cord injury in complete brachial plexus avulsion, there is regeneration from within the spinal cord to the periphery. There is limited motor plasticity during the process of recovery.

4.2. Introduction

Severe injury of the brachial plexus is the most serious of all injuries to peripheral nerves and causes grave impairment of the quality of life (Bertelli and Ghizoni, 2003; Birch, 2003; Holtzer *et al.*, 2002; Nagano, 1998; Terzis *et al.*, 2001). The incidence of these injuries is much higher today than the incidence in the past. Surgical repair of the injury was previously regarded as unfavourable and unrewarding (Bonnard and Narakas, 1995; Kawai, 2000). However, there have been considerable advances in understanding the traction injury to the brachial plexus in adults (Birch, 2003; Sunderland, 1978). With developments in anaesthesia and microsurgery, various surgical repair techniques have been adopted. These efforts have changed the previously

negative attitudes towards surgical repair, and repair of the brachial plexus by surgical procedures is now commonly practiced (Kawai, 2000).

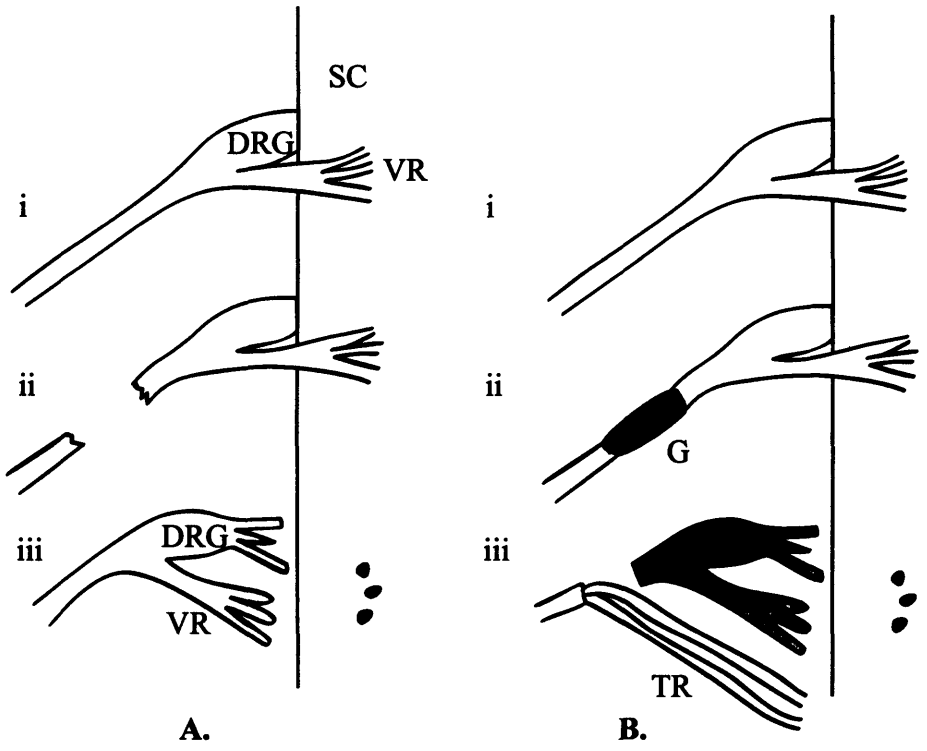
The availability of surgical repair for the traumatised brachial plexus to restore some motor and sensory function includes conventional nerve grafting, nerve transfer and noble surgical measures i.e. re-connection of avulsed spinal nerve to the spinal cord (re-implantation). When there is a segmental defect of a ruptured nerve, continuity is restored by nerve graft (Millesi, 1988; Millesi, 1997). Restitution of continuity is not always possible in cases of root avulsion and the only way to achieve neurotization could be to perform nerve transfer (Millesi, 1997). This means joining an uninjured nerve to the distal stump of injured nerve. A healthy, donor nerve is separated from its territory and its proximal stamp is then connected directly, or *via* grafts, usually to a healthy, post-lesional, distal portion of a non-functioning nerve or implanted directly into denervated muscle or insensitive skin (Narakas and Hentz, 1988) . Various donor nerves such as the accessory nerve, intercostal nerves, phrenic nerve, contralateral C7 nerve or branches of the cervical plexus can be used (Chuang, 1997). The curative surgical strategy of re-implanting avulsed spinal roots or nerve grafts back to the spinal cord has been applied to patients with severe brachial plexus injury (Carlstedt *et al.*, 2000).

Traction brachial plexus injury is usually a combined lesion: rupture in some nerves, with avulsion in some and preserved continuity in other roots (Birch *et al.*, 1998; Narakas, 1993) Figure 4.1. Operative intervention is indicated when there is evidence of section or rupture of the brachial plexus and, in closed traction lesions, surgery should be performed as soon as possible (Bonnard and Narakas, 1997). The well accepted goals of surgical repair are: reconstruction of brachiothoracic pinch, reconstruction of elbow flexion, reconstruction of a basic hand function and alleviation or improvement of pain (Bonnard and Anastakis, 2001). The results of surgical repair of brachial plexus injuries are influenced by the level and extent of injury, the type of surgical procedure (Samardzic *et al.*, 2002), and, above all, by the delay before repair (Bentolila *et al.*, 1999; Birch *et al.*, 1998).

Though it is now standard practice to repair a brachial plexus lesion (Birch, 2001; Rutowski, 1993), unfortunately it remains difficult to evaluate the result of repair because of the complexity of its anatomy and various types of lesion that are involved in traction injury (Belzberg, 2004; Boome, 1997; Sunderland, 1993). In addition, the individual efficacy of nerve transfers has not been measured objectively, thus rendering the prognostication of outcomes for these techniques a major problem (Inciong *et al.*,

2000). The present study represents an attempt to resolve the confounding issues surrounding the repair of brachial plexus injury and difficulties in assessing the outcome of the different surgical repairs. In this study evaluation of motor recovery after different surgical repairs such as nerve grafting, direct nerve transfer and re-implantation was attempted. Results were analysed critically and any regeneration was credited to the nerve repair only if there were no other possible explanations for recovery.

Figure 4.1. Schematic representation of brachial plexus injuries (A) and repairs (B).



DRG, dorsal root ganglion; VR, ventral root; SC, spinal cord; G, graft; TR, transfer. (A)Before repair: (i) intact root, (ii) rupture, (iii) avulsion. (B) After repair: (i) intact root, (ii) rupture repaired by grafting, (iii) avulsion repaired by nerve transfer (from J.S Berman *et al.* Pain 75; 1998. 199-207 with Permission).

4.3. Methods

4.3.1. Patients

Fifty one patients who had sustained brachial plexus injury with spinal nerve root avulsion were studied. Surgical procedures were performed in forty one patients according to techniques developed in the Peripheral Nerve Injury Unit (PNI) of the Royal National Orthopaedic Hospital (Birch, Bonney and Wynn Parry) (Birch, 1998) and at the Karolinska Institute (Carlstedt *et al.*, 2000; Carlstedt *et al.*, 1995; Carlstedt, 1995).Ten patients did not have any surgical repair and were treated with only conservative measures.

Age and sex

All patients who had surgical repairs were young and male. Two out of ten patients who did not have any surgical repair were female. The age of the patients and the types of surgical repairs are shown in Table 4.1.

Table 4.1. Age and type of surgical repairs.

Repairs	Age (mean± SEM) years
All types of repairs	26.7 ± 1.2
Accessory nerve to suprascapular nerve transfer	24.3 ± 1.9
C6/C6 graft and other repairs	24.3 ± 1.1
Re implantation and other repairs	27.4 ± 2.4
Patients who did not have any surgical repair	27.6 ± 3.0
P value (Kruskal-Wallis test)	0.44 (4.8)

Details of the patterns of injury and operative procedures are shown in Tables 4.2 and 4.3. Most patients had more than one type of repair operations.

Table 4.2A. Lesions of the brachial plexus who had surgical repair.

Type and level Lesion					No. of
C5	C6	C7	C8	T1	patients
A	A	A	A	A	5
A?	A	A	A	A	1
R	A	A	A	A	7
A	A	A	A	I	1
R	A?	A	A	A	1
R	R	A	A	A	9
A	A	A	R	R	1
A	A	A	LIC	LIC	1
A	A	A	I	I	1
A	A	A	DRL	DRL	1
R	A	A	A	R	1
R	A	R	R	A	1
R	A	A	I	I	1
A	A	R?	LIC	LIC	1
R	R	A	A	I	1
R	R	A	A	A?	3
R	R	A	A	Intradural lesion	1
Pre-ganglionic rupture	Pre-ganglionic rupture	LIC	A	A	1
R	A	A	Recovering	Recovering	1
R?	A	A	A?	I	1
R	A?	A?	A	A	1
TOTAL					**41**

A: Avulsion, R: Rupture, LIC: Lesion in continuity, I: Intact, DRL: Dorsal root lesion,

Table 4.2B. Lesions of the brachial plexus who did not have any surgical repair.

Type and level Lesion					No. of
C5	C6	C7	C8	T1	patients
A	A	A	A	A	3
A	A	A	?A	?A	1
A?	A?	A?	A?	?A	1
?R	A	A	A	A	1
Partial Avulsion	A	A	A	LIC	1
R	LIC	A	A	?A	1
I	I	A	A	A	1
A	A	A	I	I	1
TOTAL					**10**

A: Avulsion, R: Rupture, LIC: Lesion in continuity, I: Intact,

Table 4.3. Operative Procedures.

Methods of surgical repair	Number of patients
Accessory to suprascapular nerve transfer	15
Fasicles of ulnar nerve to nerve to biceps transfer	2
Fasicles of median nerve to nerve to biceps transfer	1
Accessory phrenic nerve to nerve to biceps transfer	1
Intercostal nerve to nerve to biceps transfer	2
Intercostal nerve to nerve to serratus anterior transfer	2
Accessory nerve to nerve to biceps transfer	1
C5/C6 graft	26
Re-implantation	8

All patients were operated on within 3 months of injury and the duration between the injury to assessment and the duration between injury to operation is shown in Table 4.4.

Table 4.4. Duration between the injury and surgery (days), Duration between the injury and assessment (years).

Methods of repair	Duration between injury and surgery (days)			Duration between injury and assessment (years)		
	*	Max	Min	*	Max	Min
XI to SS	48.5 ± 11.4	114	3	3.8 ± 0.8	10.2	1.1
Other nerve transfer	78.4 ± 31.1	217	1	2.3 ± 0.4	3.6	0.6
C5/C6 graft	39.7 ± 8.7	122	1	5.9 ± 1.1	19.3	1.1
Re-implantation	8.9 ±1.8	19	3	3.2 ± 0.4	4.2	1.6
P value	0.17			0.7		

XI; accessory nerve, SS; suprascapular nerve, Max; maximum, Min; minimum

**(values are mean ± SEM)*

There were no statistically significant differences in the mean interval between the injury and surgery in the groups of patients repaired with XI to SS nerve transfer, C5/C6 graft or re-implantation. (*P=0.17*) (Kruskal-Wallis statistic 3.56)

There was no statistical difference between the mean duration after the injury to assessment in the groups of patients who had C6/ C6 repair or re-implantation (*p=0.7*)

4.3.2 Motor assessment

All patients underwent a detailed neurological examination. Motor power in the upper limb was assessed using the grading recommended by the Medical Research Council. **Refer to Chapter III for details.**

Statistics: The data were analysed using Mann-Whitney U test and Kruskal-Wallis statistic. *P*-values <0.05 were considered to be significant. Data are presented as mean ± SEM (standard error of mean) if otherwise stated. (Refer to Chapter III).

4.4. Results

4.4.1. Clinical results of motor recovery

Motor power

The number of patients who had nerve transfer using ulnar, intercostals nerves, accessory phrenic nerve i.e. other than accessory nerve transfer was too small for statistical analysis. The motor recovery for this group varies from MRC 1 to 4 and

shown in (Table 4.5). The assessment of clinical recovery by MRC grading of muscle power from C5/6 graft and re- implantation is shown in Tables 4.6 and Figures 4.2 and 4.3. Functional recovery at the shoulder and elbow using the Narakas' functional scores is shown in Figure 4.4.

Recovery of motor function in patients who did not have any surgical repairs

In patients who did not have any surgical repairs, there was no evidence of recovery i.e. motor power or gaining any Narakas' scores except where the nerves were either intact or lesion was in continuity. They were assessed 10.8 ± 4.0 years after injury.

Table 4.5. Recovery of motor function from various nerve transfers.

Methods of surgical repair	Number of repairs	Motor power (MRC grading)	
Accessory nerve to suprascapular nerve transfer	15	3.1±0.3*	2.4±0.4§
Ulnar to nerve to biceps transfer	2	1†	4‡
Median to nerve to biceps transfer	1	3	
Accessory phrenic nerve to nerve to biceps transfer	1	4	
Intercostal nerve to nerve to biceps transfer	2	1†	2‡
Intercostal nerve to nerve to serratus anterior transfer	2	4†	4‡
Accessory nerve to nerve to biceps transfer	1	4	

*Supraspinatii *(values are mean ± SEM)*, §Infraspinatii *(values are mean ± SEM)*,

† Patients A *(absolute value)*, ‡ Patients B *(absolute value)*

Table.4.6. Recovery of motor function from C5/6 graft and re- implantation.

Methods of surgical repair	Number of repairs	Motor power(MRC grading)*			
		Pectorals	Deltoid	Biceps	Triceps
C5/C6 graft	26	3.4 ± 0.2	2.4 ± 0.3	2.0 ± 0.3	2.1 ± 0.4
Re-implantation	8	2.7 ± 0.5	1.5 ± 1.0	2.0 ± 0.5	2.2 ± 0.6
P values		0.2	0.3	1.0	1.0

**(values are mean ± SEM)*

There was no statistical difference in the motor power (pectorals, deltoid, biceps or triceps muscles) between patients who had C5/ C6 graft and those with re-implantation (Mann Whitney U test).

Figure 4.2. Recovery of motor function from C5/C6 repair.

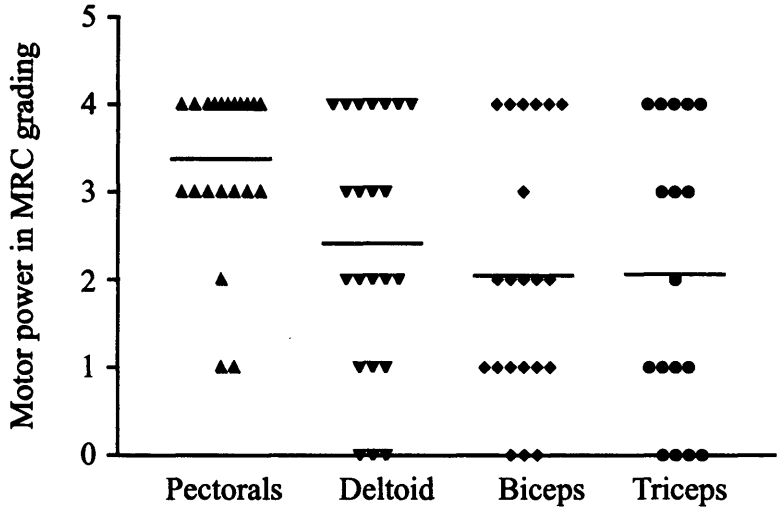


Figure 4.3. Motor recovery from re-implantation.

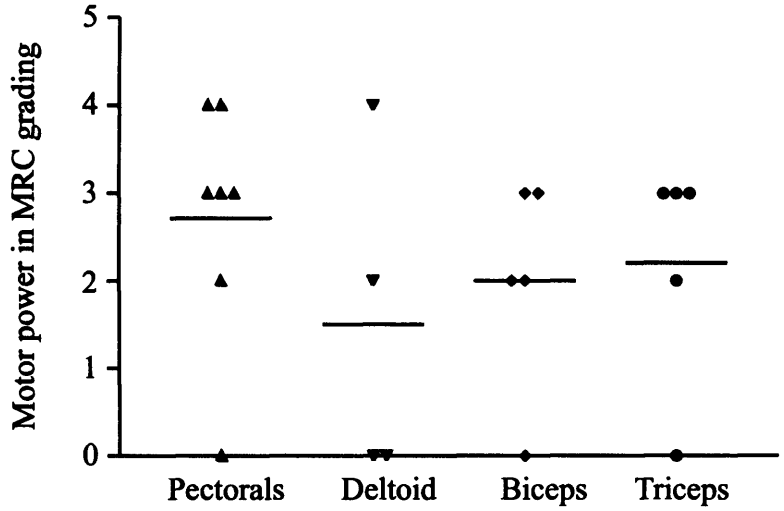
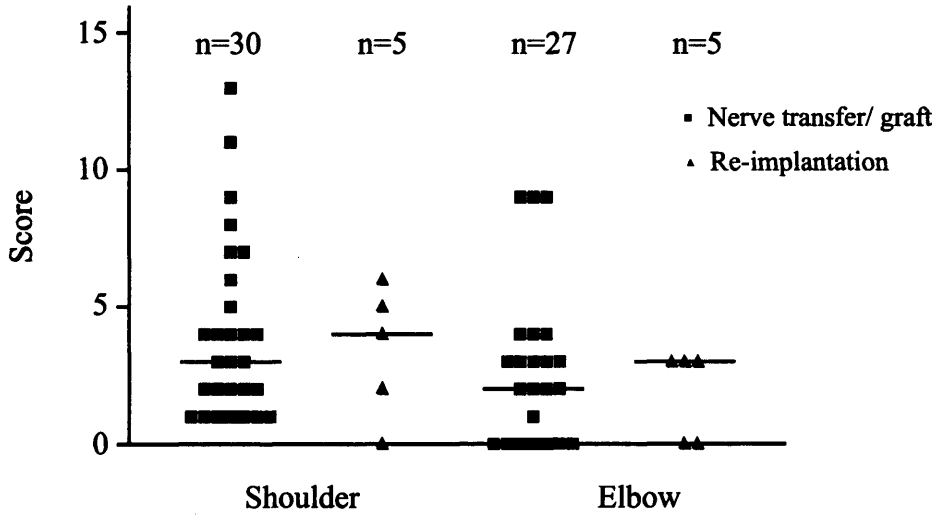


Figure 4.4 Narakas' functional scores.



There was no statistical significant difference in Narakas' functional score for the shoulder or elbow in patients repaired by re-implantation or other surgical measures (shoulder $P = 0.94$ and elbow $P = 0.98$); (Mann Whitney U test).

4.4.2. Results of Neurophysiological examination

EMG examination

Needle EMG examination of affected muscles showed only spontaneous activity in the form of fibrillations and positive sharp waves or features of re-innervation. Early re-innervation was associated with small amplitude, poly-phasic motor units. As re-innervation became more established, larger motor units with broad and poly-phasic morphology were recorded. At times, only single motor units, firing at higher rates were seen and the interference pattern on maximum voluntary effort varied from much reduced to moderately reduced.

Motor unit potentials (MUPs), firing synchronously with respiration (inspiration) during quiet or voluntary breathing, were observed in several cases and these same motor units could be activated also by volitional contraction. Contractions of limb muscles in synchrony with respiration have been termed the "breathing arm". Attempts to move the arm very often result in co-contraction of agonist and antagonist muscles. The "breathing arm'' and co-contraction is discussed in the next chapter.

Trans-cranial Magnetic stimulation study (TMS)

The amplitudes of the motor responses (where present) were smaller and the latencies of the responses were prolonged on the injured side compared to the contra-lateral side regardless of the surgical repair method used. However, in a few patients, the motor evoked potentials of proximal muscles had larger amplitude and longer latency on the injured side when compare to the contralateral (normal) side. An example of the motor evoked responses are shown in Figure 4.5 A and B. The values of absolute amplitude and latency of biceps motor responses recorded on the injured sides of patients repaired by graft and re-implantation compared to the unaffected contralateral side are shown in Table 4.7 and Figures 4.6 A and B and 4.7 A and B. The difference of amplitude and latency of contralateral and injured sides are also shown in Table 4.8 and Figure 4.8.

Figure 4.5. Motor responses from trans-cranial magnetic stimulation of the unaffected **(A)** and affected **(B)** side. Note the reduced amplitude and increased latency of the responses from muscles on the affected side.

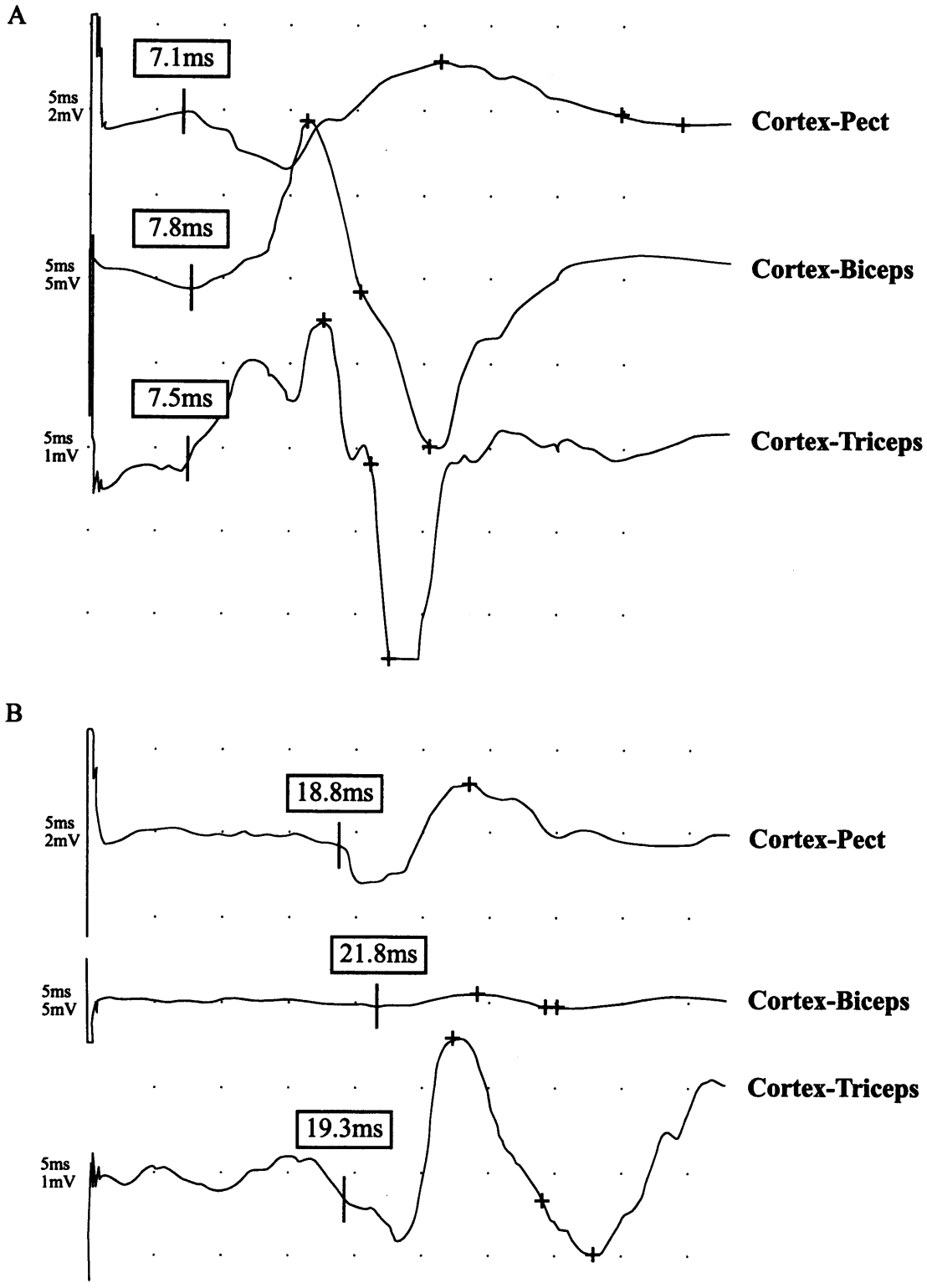


Table 4.7. Absolute amplitude and latency of biceps motor responses in patients repaired by graft and re-implantation.

	C5/6 Graft		Re-implantation	
	Amplitude (mV; mean ± SEM)	Latency (m; mean± SEM)	Amplitude (mV; mean ± SEM)	Latency (ms; mean ± SEM)
Contralateral	5.0±1.0 (n=18)	11.8±1.5 (n=18)	3.0±1.2(n=5)	10.4±1.1(n=5)
Injured	1.3±0.3 (n=19)	17.2±1.4 (n=17)	0.4±0.1(n=5)	17.3±2.0(n=5)

There was no statistically significant difference of absolute amplitude (*p=0.08*; Mann-Whitney U test) or absolute latency (*p=0.81*; Mann-Whitney U test) of biceps motor response on the injured side in patients repaired by C5/C6 graft or re-implantation.

Figure 4.6. Absolute amplitude study.

Figure 4.6A. Amplitude of motor response of biceps in patients repaired by C5 and C6 graft.

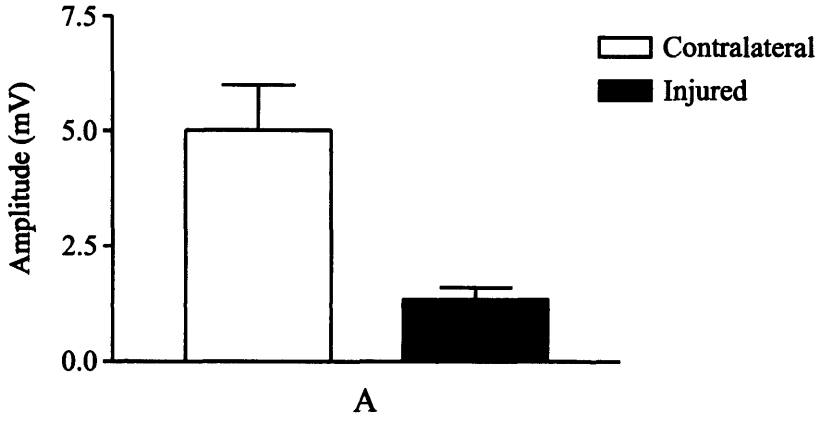


Figure 4.6B. Amplitude of motor response of biceps in patients repaired by reimplantation.

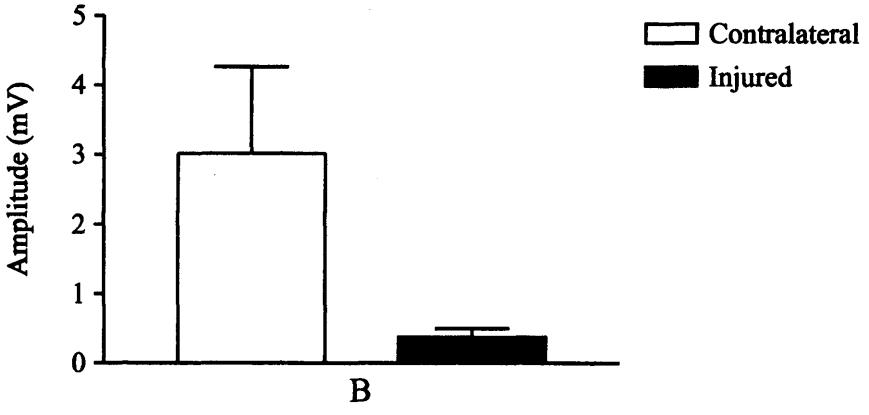


Figure 4.7. Absolute Latency study.

Figure 4.7A. Latency of motor response of biceps in patients repaired by C5 and C6 graft.

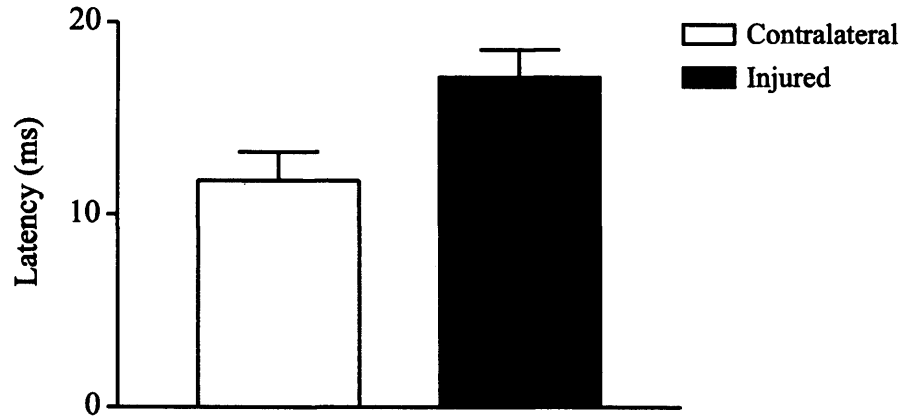


Figure 4.7B. Latency of motor response of biceps in patients repaired by reimplantation.

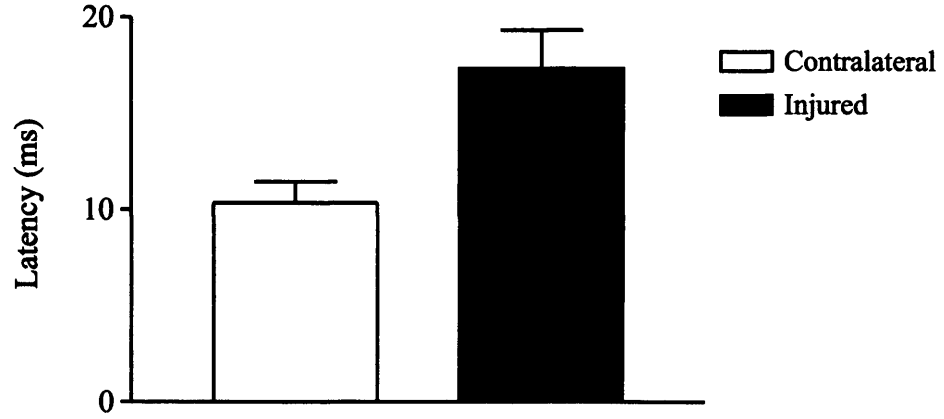
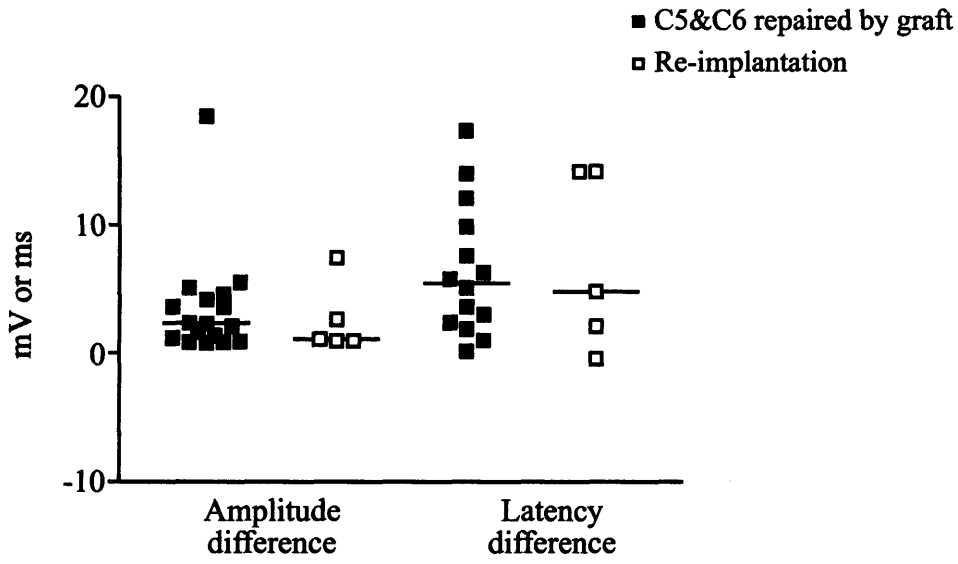


Table 4.8. Difference of Amplitude and latency in biceps motor responses of patients repaired by C5/C6 graft and re-implantation.

	C5/6 Graft		Re-implantation	
	Amplitude difference	Latency difference	Amplitude difference	Latency difference
Number	17	5	14	5
Means	3.5±1.0	2.6±1.2	6.5±1.4	7.0±3.1

Patients repaired by C5/C6 graft or re-implantation showed no statistically significant difference in differences of amplitude (p=0.75; Mann-Whitney U test) and latency (p=0.96; Mann-Whitney U test) of biceps motor responses.

Figure 4.8. Amplitude and Latency differences of Motor response of biceps in contra-lateral (non injured side) and injured side in patients repaired by nerve graft or re-implantation.



4.5. Discussion

Motor recovery

Indications for each surgical procedure depend on the following factors: the degree of damage, the site of injury, the type of involved roots, the time interval between injury and operation, the patient's age, sex, and occupation. These factors are also important to determine the prognosis (Nagano, 1998; Terzis *et al.*, 2001).

In this study, it seems that the results of accessory nerve to supra-scapular nerve transfer gained a moderate recovery of shoulder function. Meta analysis has shown that the spinal accessory nerve was used in 41% of repairs to restore shoulder function and that 98% of these operation achieved ≥M3 shoulder abduction and better than intercostals nerve transfer (Merrell *et al.*, 2001). Chantal Bonnard and Algimantas O. Narakas found that 57% of this transfer procedure produced useful result as well (Boome, 1997). However, since these studies showed recovery as percentage of muscles achieving M3 strength it is difficult to compare accurately results in the present and other studies (Midha, 2004).

Since there were only limited number of patients (n=8) in this study who had nerve transfer using various donor nerves with very limited numbers in each group, it may not be logical to draw conclusions. Never the less, findings in this study seem to be similar to previous studies. In this study, ulnar nerve to nerve to biceps nerve transfer (Oberlin's) was performed in only 2 patients and one of those patients was assessed very early and recovery may continue (Sungpet *et al.*, 2000). According to Gu and Ma, phrenic nerve transfer is found to be effective (Gu, 1989; Gu *et al.*, 1989; Gu *et al.*, 1990; Ma *et al.*, 1998) . Only one patient in this study was repaired using the accessory phrenic nerve to restore elbow flexion and with a good result achieving a biceps strength 4 by MRC grading. Two patients had intercostal nerve to long thoracic nerve transfer from which the outcome was good in both cases and consistent with other studies.(Birch, 2001; Nagano *et al.*, 1992; Nagano *et al.*, 1995) Accessory nerve to nerve to biceps transfer also produced a good recovery, achieving a power of biceps muscle to MRC grade 4. Two patients had intercostal nerve to nerve to biceps transfer but the outcome was poor. Songcharoen *et al* concluded that the result from the transfer of accessory nerve to musculocutaneous was comparable to other types of neurotization (Songcharoen *et al.*, 1996) and Waikakul *et al* also found that spinal accessory nerve transfer had a better motor outcome than intercostal nerve transfer (Waikakul *et al.*, 1999) . The conclusion of the meta analysis ,however, found that direct intercostal nerve transfer obtained better result than spinal accessory nerve transfer (Merrell *et al.*, 2001). Other studies have found also that accessory nerve to musculocutaneous nerve transfer can produce excellent results but can cause a high failure rate (Boome, 1997).

Allieu *et al* concluded that nerve repair using nerve graft from a non-avulsed root gives better functional scores than nerve transfer from intercostal or spinal accessory nerves using inter-positional nerve graft. In their series, the average functional score for the elbow flexors was 4.4 out of a possible 11 with 66% of patients having a strength recovery of M3 or more (Allieu *et al.*, 1997) . In this study, the Narakas' functional score for the elbow was 4 out of possible 9 in 40.7% of patients. However, only 33.3% of patients achieved M3. Again accurate comparison of these results is made difficult because of different mechanisms of injury in the study population, different donor nerves were used for the graft or transfer, a different timing of assessment was used and a different method for showing the results (Dubuisson and Kline, 2002; El-Gammal and Fathi, 2002; Kim *et al.*, 2003; Ochiai *et al.*, 1996; Samii *et al.*, 2003; Tung *et al.*, 2003).

Though nerve transfer definitely has a role in the management of brachial plexus lesion (Narakas, 1982; Narakas and Hentz, 1988), in patients with multiple nerve root avulsion, this option is limited because the number of nerves needing repair is always out-numbered by available donor nerves. One spinal nerve may have twenty five to thirty five thousand myelinated fibres whilst one intercostal nerve may have less than a thousand. There are simply not enough resources for nerve transfer. For those patients who have multiple nerve root avulsion, the surgical strategy of re-implanting avulsed spinal roots or nerve grafts to the spinal cord was applied. This approach followed a long series of laboratory investigations including studies in primates (Carlstedt, 1997; Carlstedt *et al.*, 1986; Carlstedt *et al.*, 1993; Cullheim *et al.*, 1989; Hallin *et al.*, 1999; Smith and Kodama, 1991). A follow up study of the first ten re-implanted cases showed that three patients regained some useful function (Carlstedt *et al.*, 2000). There was, in most cases, signs of regeneration of motor fibres from spinal cord to proximal arm muscles and some recovery of muscle activity (Bertelli and Ghizoni, 2003; Carlstedt *et al.*, 2000; Carlstedt *et al.*, 2004; Holtzer *et al.*, 2002). In this study, motor recovery in patients repaired by re-implantation is comparable to those who had C5/C6 repair. In addition, the recovery of shoulder and elbow function, as assessed by Narakas' functional score, appears similar in both these surgical procedures. Although there is no statistically significant difference of the Narakas' function scores between these surgical methods, patients who had C5/C6 repair can potentially achieve a higher score of functional gain since intraspinal repair of brachial plexus avulsion is hampered by muscle co-contraction (Carlstedt *et al.*, 2004). It was possible to verify these clinical observations by neurophysiological investigation. Trans-cranial magnetic stimulation demonstrated connectivity from motor cortex to muscle. There were no statistically significant differences of absolute amplitude and latency of the motor evoked responses nor were there differences of the motor responses of contralateral (normal) side and injured side in muscles of patients repaired by C5/C6 graft compared to re-implantation. The explanation for the bigger motor evoked potentials of proximal muscles was probably due to deafferentation as can be seen in amputations because more motorneurons are recruited in the proximal muscle of the deafferented body part (Cohen and Mano, 2002).

In this study, though comparison of the recovery of motor function of different studies is impossible, we can compare the results of surgical repairs among our patients who had matched age, sex, and duration of delay between injury and operation as well as

duration between injury and assessment. All patients were operated by two leading world experienced peripheral nerve surgeons (RB &TC), who share similar management strategies. It seems that motor recovery in the proximal limb following re-implantation in patients with avulsion is similar to that achieved after nerve transfer and grafting. The successful outcome after re-implantation seems to be due to swift intervention although there are many other factors which could influence the regeneration of motor neurons (Bentolila *et al.*, 1999; Kawai *et al.*, 1988; Kim *et al.*, 2003; Narakas, 1984).

Re-implantation of avulsed spinal nerve root is a new surgical measure and there is, therefore, not surprisingly, some scepticism regarding its use (Bertelli and Ghizoni, 2003; Holtzer *et al.*, 2002; Kline, 2000; Thomeer *et al.*, 2002). Although neurotization or nerve transfer has become a standard surgical measure, initially this procedure also faced similar doubt and Narakas stated that the role of nerve transfer is limited and at an experimental stage however, he concluded later that this method is complementary to other methods of repair in brachial plexus injury (Narakas, 1984; Narakas and Hentz, 1988). It must be remembered that neurotization or nerve transfer is a palliative procedure that leaves the pertinent spinal cord segment separated from the periphery thus leading to neuronal death. With increasing knowledge in molecular biology regarding spinal cord injury in repair, there will be the possibility of a better outcome in future management of brachial plexus injury with re-implantation.

Technical limitation of the study

Examination of brachial plexus muscles and locating the level of lesion through knowledge of their common supply are inadequate and complex (Birch *et al.*, 1998; Lee *et al.*, 1992) . There is a possibility that source of innervation may be from the multiple components of brachial plexus, which contribute to the recovery of given muscles. However, this potential pitfall can be minimised by intra-operative diagnosis and intra-operative electrical monitoring.

Manual examination of motor power testing appears crude and one might be concerned for its consistency and accuracy (Wiles *et al.*, 1992). However, this method has proved to be fairly accurate (Jepsen *et al.*, 2004) and has been widely used to assess functional recovery for the surgical repairs discussed above and in other clinical trials (Bromberg, 2002). Although EMG and nerve conduction studies are sensitive and could detect re-innervation, findings from neurophysiological examination are poorly related to

functional recovery and there are also technical limitations especially for proximal muscles (Bromberg, 2002; Tsai *et al.*, 2002).

Using the TMS, the entire motor pathway can be assessed, which is valuable for the verification of clinical observations. However, the response can be modified by plasticity of the nervous system as a result of deafferentation and it therefore has limited value in quantification of functional recovery. In addition, in any assessment of functional connectivity, it is important to bear in mind that muscles will very often be atrophic which can alter the characteristics of the motor evoked response (Lissens and Vanderstraeten, 1996).

Conclusion:

Management of brachial plexus injury is one of the most challenging for the peripheral nerve surgeon. Because of the complexity of the injury, there is much disagreement about management strategies (Belzberg, 2004). In this study, for the first time, we have attempted to evaluate the functional recovery of different surgical measures in biologically close matched groups of patients. We demonstrated that each surgical measure is valid in its own merit provided that a logical approach to the individual type of injury is made and followed by swift action. Re-implantation of the avulsed spinal nerve root is a reasonable surgical procedure in management of severe brachial plexus injury and will pave the way for further understanding of central nervous system injury and regeneration.

Chapter V: Long term outcome of functional recovery in patients repaired by re-implantation

5.1. Summary

Nine cases of complete brachial plexus injury with 3-5 spinal nerves avulsed from the spinal cord were studied after ventral root re-implantation to the spinal cord. A detailed long term follow up was based on clinical and electrophysiological findings during recovery. Muscle activity started about one year after surgery in the shoulder.
After two years, there was recovery into upper arm muscles and after a further year activity was noted distal to the elbow. In younger individuals hand function can be restored. Synkinesis which disturbed function was frequent and occurred in patients with a good muscle recovery. The phenomenon of contractions of limb muscles in synchrony with respiration referred as "breathing arm" occurred in some patients. There was little recovery of sensory function. There was alleviation of pain in parallel with the return of function.

The efficacy of intra spinal repair of a complete brachial plexus avulsion injury was comparable to that achieved from reconstruction of a less severe, brachial plexus injury of upper spinal nerve ruptures and lower root avulsion except in younger individuals where hand function also can be restored.

5.2. Introduction

In most cases of severe brachial plexus injury, one or several spinal nerve roots are torn from the spinal cord. The root avulsion injury is a "longitudinal" spinal cord injury that interrupts the segmental spinal cord circuits and cause nerve cell death. Survival of neurons and axonal regrowth within the spinal cord is necessary for regeneration of function. Therefore, in contrast to extra spinal plexus injuries, root avulsions or "pre ganglionic" injuries have been considered impossible to repair (Seddon, 1972). Several, palliative procedures including nerve transfers have been developed to compensate for function in avulsed roots (Narakas, 1984). Neighbouring intact nerves, for example the accessory nerve, intercostal nerves, phrenic nerves and even nerves in the contra-lateral, uninjured brachial plexus are used (Gu *et al.*, 1991).

The first description of root avulsion in brachial plexus injury was by Flaubert (Flaubert, 1827; Holtzer *et al.*, 2002; Robotti *et al.*, 1995) and the first exploration of a

brachial plexus injury with root avulsions, by means of laminectomy, was performed by Frazier and Skillern in 1991 (Frazier and Skillern, 1911).Their case report still remains up to date with a clear description of the severe pain experienced by the patient after such a lesion as well as advocating an early intervention (10 days after injury).
A rupture of the efferent or motor root is similar to an injured peripheral nerve and therefore, if repaired, can give rise to functional recovery (Carlstedt and Noren, 1995). Even if the rupture occurs at the ventral root - spinal cord junction i.e. the transitional region between the peripheral (PNS) and central (CNS) nervous system, there are possibilities for regeneration of interrupted motoneuron axons into the growth promoting PNS (Richardson *et al.*, 1980).In a long series of animal experiments from several laboratories, it has been documented that re-implantation of avulsed ventral roots leads to a return of function (Cullheim *et al.*, 1999).This surgical strategy has been applied for some time in humans with complete avulsion injuries to the brachial plexus (Carlstedt *et al.*, 2000; Carlstedt *et al.*, 1995).It must be kept in mind, however, that any surgical manipulation of the spinal cord carries with it the risk of injuring long tracts (Carlstedt *et al.*, 2000; Holtzer *et al.*, 1996) and this surgical method should be reserved for the most severe cases.

Direct reconstruction of the connections between the spinal cord and peripheral nerves, by implanting or re-attaching avulsed dorsal roots to the spinal cord, was first reported by Bonney and Jamieson (Bonney and Jamieson, 1979) in a case of brachial plexus lesion. Return of functional after re-implantation of avulsed ventral roots into the spinal cord was first reported in 1995 (Carlstedt *et al.*, 1995).Since then, intra-spinal repair of brachial plexus injuries have been reported from 3 institutions world wide (Bertelli and Ghizoni, 2003; Carlstedt *et al.*, 2000; Carlstedt *et al.*, 1995; Fournier *et al.*, 2001; Fournier *et al.*, 2005).
In previous reports, regeneration and reconnection with proximal arm muscles was demonstrated after repair of ruptured nerve roots or implantation of avulsed ventral roots or nerve grafts into the spinal cord. In some of these patients, useful return of function was regained in the shoulder and proximal arm muscles (Carlstedt *et al.*, 2000; Carlstedt *et al.*, 1995). In a recent case report, recovery of hand function was reported in a pre- adolescent young boy after complete C5-T1 avulsion injury and re-implantation to the spinal cord (Carlstedt *et al.*, 2004).
This present study is a detailed, long term follow up report of patients with complete brachial plexus injuries based on clinical and electrophysiological findings during

recovery. The efficacy of the intra-spinal repair of complete brachial plexus avulsion is revealed as an outcome similar to that is achieved after reconstruction of a less severe brachial plexus injury of rupture of the upper spinal nerve and lower root avulsion.

5.3. Methods

5.3.1. Patients

Nine patients who had sustained brachial plexus injury with spinal nerve root avulsion were studied.

Age and sex

All patients were studied between 60days and 6.86 years after injury (2.17 ± 0.46) years. All patients were males and mean age at the time of injury was 26.86 ±2.14 years (Table 5.1). The patients were assessed in a total of 30 occasions.

The age of the patients and the types of surgical repairs are also shown in Table 5.1.

Table 5.1. Injury and repair.

1 PB	26.9,M	11	Avulsion C5 - T1,	Implantation of grafts to C5-C8 and 1 graft dorsal spinal cord at C7 segment
2 DB	24.5,M	22	Avulsion C5 - T1	XI to SS.Implantation of grafts to C5,C6,C7& C8
3 SB	19.4,M	19	Avulsion C5 - T1	Implantation of grafts to C5,C6 & C7
4 MB	32.4,M	6	Avulsion C5 – C7, rupture C8 & T1	Implantation of graft C5, C6, C7 and grafting lower trunk
5 SE	17.5,M	11	Avulsion C6-T1, rupture C5	XI to SS, C5 to upper trunk graft, Implantation of grafts to C6 &C7
6 PH	35.5,M	3	Avulsion C6-T1 Rupture C5	Repair C5.Implantation of grafts to C7, C8, T1.Implantation to dorsal spinal cord C7 segment
7 JJ	27.6,M	4	Avulsion C5 - T1, with rupture of C6 ventral root	Implantation of graft to C5, C6 and C7, one graft to proximal stump of C6 ventral root
8 IT	35.5,M	6	Avulsion C7-T1, rupture roots to C5 and C6	Implantation of nerve grafts connected to all ventral roots.
9 WH	9.2, M	24	Avulsion C5-T1	Implantation of the grafts to ventral roots to C5,6,7,8 & T1. One motor nerve of cervical plexus grafted to motor root of C5, XI to SS transfer, sensory branch of supraclavicular nerves to sensory parts of C7, C8, T1

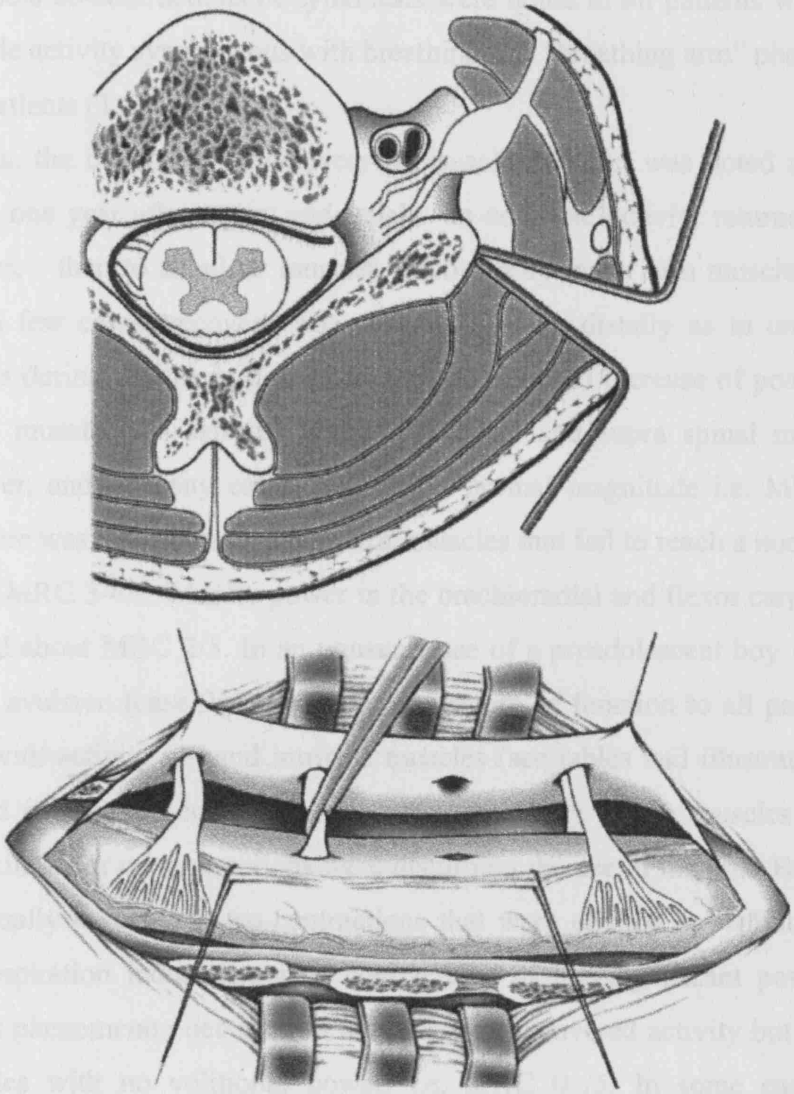
5.3.2. Surgery: Patients were operated within 3 to 24 days after trauma (Table 5.1). Surgical procedures were performed according to techniques described by Carlstedt *et al* (Carlstedt *et al.*, 2000) Figure 5.1. In 4 cases, intra-spinal exploration and repair were preceded by an extra-spinal exploration of the brachial plexus on separate occasions. Patients were positioned laterally on the operating table to allow for a simultaneous approach to the extra - as well as intra-spinal parts of the brachial plexus. Nerve grafts were distally connected to the motor parts of the upper, middle and lower trunks of the brachial plexus. Re- implantation into the spinal cord was performed at three levels for C5, C6 and C7 and in one case at four levels C5-C8. In some cases nerve transfer was performed (Table1). The dura was closed and the wound was closed in layers. Then neck was immobilised in a hard collar and the arm immobilised in a sling for six weeks of post-operative period.

5.3.3. Methods of assessment

Please refer to the Previous Chapter III.

Statistics: Data were analysed statistically using the Mann-Whitney U test and Kruskal-Wallis statistic. *P*-values <0.05 were considered to be significant. Data are presented as mean ± SEM (standard error of mean) when otherwise stated. (Refer to Chapter III).

Figure 5.1. *Upper:* Schematic drawing of a transverse section through the lower part of the neck illustrating the far lateral approach to the cervical spine. The spinal nerve roots have been avulsed from the spinal cord and from the sub-dural space.
Lower: Schematic drawing depicting the exposed spinal cord after a lateral approach and a hemilaminectomy. The dura mater is opened, and by the stay sutures in the denticulate ligament, the spinal cord has been rotated slightly to access its ventral part. Though slits in the pia mater and spinal cord surface, nerve grafts are implanted superficially into the spinal cord. (Pictures taken from Carlstedt T *et al.* Spinal nerve root repair and reimplantation of avulsed ventral roots into the spinal cord after brachial plexus injury. J Neurosurg 2000; 93: 237-47 with permission).



5.4 Results

The results shown and discussed in this chapter inevitably show some overlap with Chapter IV.

5.4.1. Clinical

Pre-operatively, all patients had total paralysis in the injured upper extremity. At surgery it was noted that in 5 patients all roots from C5 to T1 had been avulsed. In 2 patients there were intradural ruptures of C5 and C6 together with avulsions of C7-T1 and in one patient the lower spinal nerves, C8 and T1, were ruptured with avulsions of C5-C7 (Table 1). Restoration of muscle function occurred in all patients. In four patients there was useful recovery with muscle power in multiple muscles being MRC 3 or more. Muscle co-contractions or synkinesis were noted in all patients with useful recovery. Muscle activity synchronous with breathing i.e. "breathing arm" phenomenon was seen in 7 patients (Table 5.2).

In most patients, the beginning of recovery of muscle function was noted as muscle twitches within one year after injury and repair. In addition, activity returned first to pectoral muscles, then to shoulder muscles, followed by upper arm muscles about a year later. In a few cases, recovery was observed, as far distally as to one or two forearm muscles during the third year. There was an eventual increase of power in the shoulder girdle muscles i.e. serratus anterior, pectoral and supra spinal muscles to significant power, and in many cases, reaching a normal magnitude i.e. MRC 4-5/5 (Table 5.2). There was less power in upper arm muscles that fail to reach a normal but a useful level i.e. MRC 3-4/5. Muscle power in the brachioradial and flexor carpi radialis muscles reached about MRC 2/5. In an unusual case of a preadolescent boy with total brachial plexus avulsion (case 9, WH), there was return of function to all parts of the arm and hand with activity in hand intrinsic muscles (see tables and illustrative cases below). Isolated contraction could not be performed in any of the muscles that had recovered. Synkinesis or co-contractions were disturbing the use of the arm. Biceps and triceps were usually involved in co-contractions that were elicited by volitional limb movements. Respiration induced muscle contractions of non-significant power were also noted. This phenomenon occurred in muscles with recovered activity but was also noted in muscles with no volitional power, i.e. MRC 0 /5. In some cases, limb movement can be seen in synchrony with respiration or in other cases, merely a rippling of muscles under the skin. The breathing related muscle contractions were mainly found during inspiration, but occasionally also during forceful expiration and

coughing. The pectoral, deltoid, biceps and triceps muscles, i.e. muscles innervated from the C5 and C6 spinal cord segments showed respiratory synkinesis. "Breathing arm" activity did not conform to the pattern of volitional induced synkinesis. For example, in patients with co-contractions between biceps and triceps, breathing related muscle activity appeared only in biceps muscle (Table5 .2). Respiratory-induced muscle activity did not appear in muscles distal to the elbow. Patients with the best functional outcome had co-contractions but not always a "breathing arm" phenomenon (Table5. 2). Muscle synkinesis did not disappear over time. The regained function in the injured arm in the best recovery case could only serve to support activity in the intact arm since there was little recovery of sensation and also disturbance from synkinesis. The functional or useful outcome of muscle recovery was approximately 30% to 50% of normal values (according to the Narakas scoring system) for shoulder and elbow function respectively. Those values are similar to the outcome from nerve transfers or repairs in cases of complete brachial plexus injury.

There was limited return of sensation after root re-implantation even in cases where dorsal roots were re-connected to the dorsal part of the spinal cord. In many cases, there was some return of perception at the shoulder and outer aspects of the upper part of the arm corresponding to C5-C6 dermatomes. Assessment of different sensory modalities showed slight improvements in monofilament threshold as well as in cold and warm thresholds in the C5 dermatome (cases 2,8). Referral of sensation was noted in 6 patients (cases1,3,4,6,7,9).Touch of the injured arm referring to the trunk or face ("right way") and touch of the trunk or face referring to the arm ("wrong way") was noted in four patients.

Typically avulsion pain changed with the return of motor function to be confined to that part of the extremity. Usually the hand which had not recovered function, pain intensity was not changed. In one case (case 9) of regeneration throughout the arm and hand there was also complete alleviation of pain.

Table 5.2. Recovery of motor function after different follow up times and the occurrence of co-contractions and "breathing arm" phenomenon.

Case No	Durations after repair (yrs)	Muscle Power																	
		SA	PM-CL	PM-ST	SS	IS	LD	D	B	T	BR	ECRL	SUP	ECU	EDC	FCR	FCU	FDP	Int
1	4.08							0	0	0	0	0	0	0	0	0		0	0
	6.86	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0
2	0.18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0
	1.04			2				3	0	0	0	0	0	0	0	0		0	0
	1.70								1										
	3.20								1	1									
	4.68		4bc					4	3bc	3bc				0	0	0		0	0
3	0.18	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0
	4.85	5	3bc	3bc	3c	3	3	2c	2bc	3c	0	0	0	0	0	0		0	0
4	1.09	3	4c				3			3									
	1.77	5	2c	2c	2	2	3	0	2c	3c									
5	1.59	3	3	3	4		3	4											
6	0.14	1	3																
	2.65	3	3bc						1bc										
	4.09	3	3bc	3bc		0			1bc	2c			0						
7	1.14	5	0	0	0	0		0	0	0			0						
	2.01		1																
	3.17																		
		5	4	4	3	2	3	2bc	3bc	2bc						1			
	3.38	5	4	4	3	2	3		3bc	3bc									
	3.50	5	4	4			2		3bc										
	4.33	5	5c	5c	5		2		3bc							1			
8	1.99	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0		0	0
	5.22	4	1	2	0	0	2	0	0	1	0	0	0	0	0	0		0	0
9	2.0	5	5cb	5cb			4c	5cb	4cb	2cb	0	0	0	0	0	3c	4cb	4cb	2cb

SA; serratus anterior, PM-CL; pectoralis major (clavicular head), PM-ST; pectoralis major (sternal head), SS; supraspinatus, IS; infraspinatus, LD; latissimus dorsi, D; deltoid, B; biceps, T; triceps, BR; brachioradialis, ECRL; extensor carpi radialis longus, SUP; supinator, ECU; extensor carpi ulnaris, EDC extensor digitorum communis, FCR; flexor carpi radialis, FCU; flexor carpi ulnaris, FDP; flexor digitorun profundus, Int; Intrinsic muscles of the hand, c; co-contraction, b; "breathing arm"

5.4.2. Electrophysiology

EMG recordings of deltoid and biceps muscles showed motor unit potentials (MUPs) firing in volitional contraction. In 5 patients, MUPs were firing synchronously with breathing. Co-contractions were also recorded in between various muscles but co-contraction on volitional limb movements did not always co-contract with breathing. Transcranial Magnetic Stimulation (TMS) showed a delayed in latency about 50% in the shoulder and upper arm muscles in injured compared with the contra-lateral uninjured arm. The amplitude of the muscle response was significantly reduced in injured compared with the contra-lateral side.

Figure 5.2. Electromyography studies. *Upper:* Motor unit potential recorded from the abductor digiti minimi (ADM) muscle on maximal voluntary effort. *Centre*: Multichannel EMG recording of co-contracting muscles in the right upper limb (amplitude 0.5 mm/ division, latency 160 msec/ division). *Lower:* Multichannel EMG recording of contracting muscles in the right upper limb showing bursts of motor units firing synchronously with inspiration. An electrocardiographic artefact is also seen (amplitude 0.5 mm/ division, latency 2 seconds/ division). (Pictures taken from Carlstedt T *et al*. Restoration of hand function and so-called "breathing arm" after intraspinal repair of C5-T1 brachial plexus avulsion injury. Case report. Neurosurg Focus 2004; 16: E7).

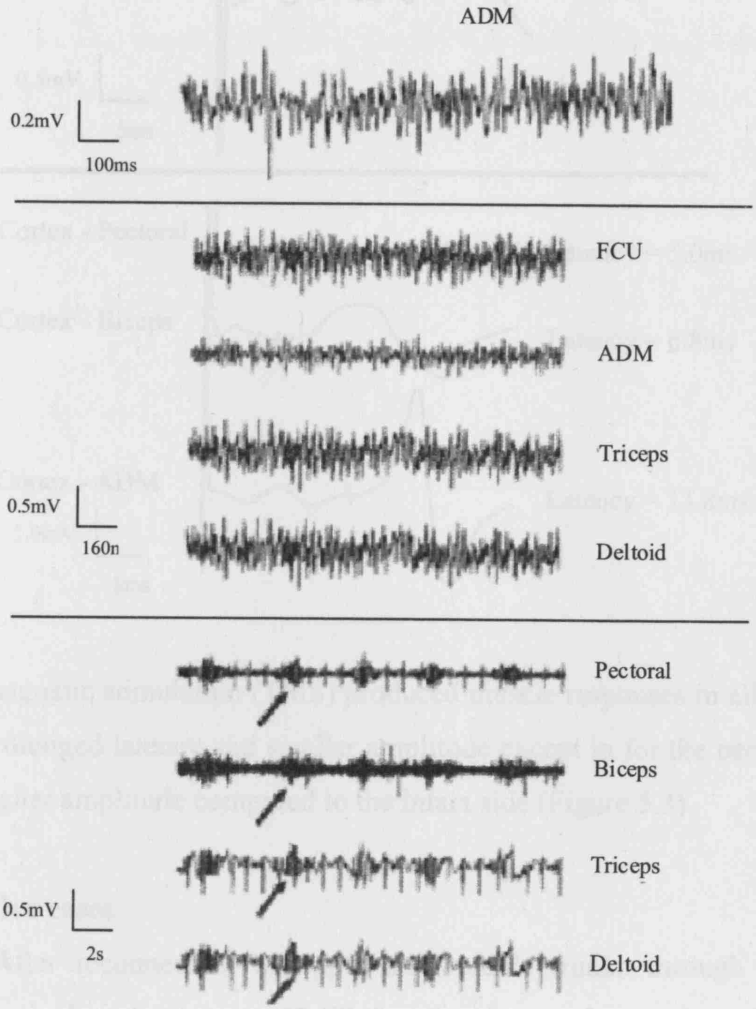
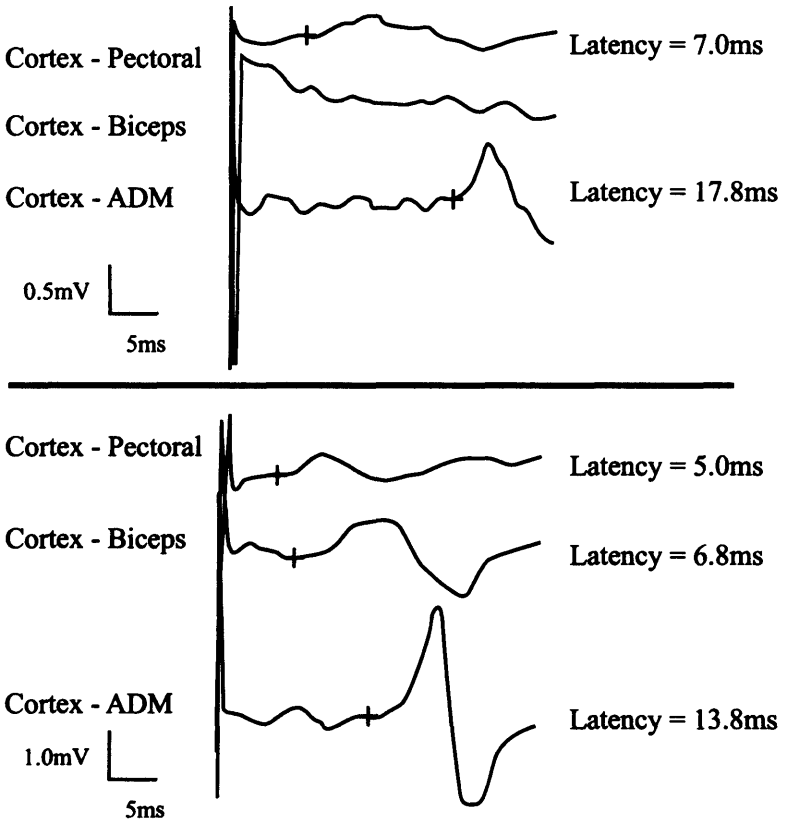


Figure 5.3. *Upper:* Motor responses from transcranial magnetic stimulation from the affected side: *Lower:* Motor responses from transcranial magnetic stimulation from the unaffected side. Note the reduced amplitude and increased latency of response from the abductor digiti minimi (ADM) on the affected side. (Pictures taken from Carlstedt T *et al.* Restoration of hand function and so called "breathing arm" after intraspinal repair of C5-T1 brachial plexus avulsion injury. Case report. Neurosurg Focus 2004; 16: E7).



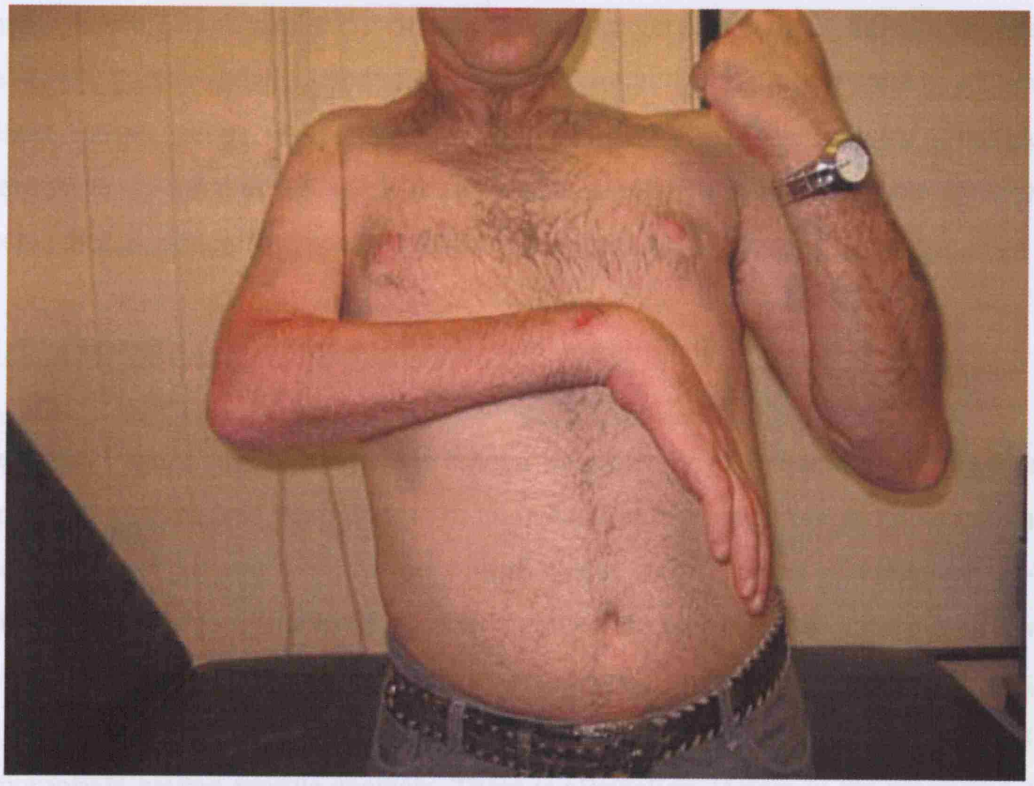
Transcranial magnetic stimulation (TMS) produced muscle responses in all of the above muscle with prolonged latency and smaller amplitude except in for the pectoral muscle, which had a higher amplitude compared to the intact side (Figure 5.3).

5.4.3. Illustrative cases

Case 7, JJ: After reconnection of upper and middle trunks through nerve grafts implanted into spinal cord segments C5-C7, functional return began about 10 months post operatively among proximal arm muscles. Three years after surgery normal power in pectoral and shoulder muscles was regained. Sub normal power in elbow flexion and extension was noted (Fig 5.4). There was sub clinical activity, 1/5 in the flexor carpi radialis (FCR) and co-contractions between biceps and triceps. Inspiratory related contractions in the pectoral and biceps muscles were noted (Table 5.2).

Touch sensation was limited to the shoulder and upper medial part of the arm i.e.C5 and T2 with normal perception of joint position in the shoulder and some joint sensation in the elbow. There was no sensation distal to the elbow, and a constant excruciating, burning and pulsing pain in the hand with no pseudomotor function in the hand.
Electromyography showed no muscle unit potentials (MUP) in the deltoid or biceps muscles 6 months post surgery. After 3 years surgery there was normal looking MUP on voluntary contraction in the biceps and pectoral in addition to small, MUP on voluntary contraction in the deltoid, triceps, infraspinatus and long flexors of the forearm. There were co-contractions between biceps-triceps and pectoral muscles. Normal inspiration induced MUPs in the deltoid, triceps and biceps occurred but this muscle activity was not strong enough to produce movements.
Transcranial Magnetic Stimulation (TMS) produced reduced amplitude and with longer latency responses in biceps and pectoral muscles of than on the intact side.

Figure 5.4: Patient (JJ) was attempting to flex both elbows (The right side is injured).



Case 9,WH: All parts of the avulsed brachial plexus were been reconnected through nerve grafts implanted into the spinal cord segments C5-C8. The accessory nerve was transferred to the suprascapular nerve. A motor branch from the cervical plexus was transferred to the upper trunk and supraclavicular sensory nerves were joined to the sensory parts of spinal nerves C7, C8 and T1.

Muscle recovery began at approximately 8-10 months post operatively for the shoulder and elbow. After two years post operatively there was normal power (5/5) in the trapezius and serratus anterior muscles. Sub normal power (4/5) was noted in the deltoid and biceps muscles as well as in forearm wrist and finger flexors. There was some function (1-2/5) in the triceps and intrinsic hand muscles but no clinical function in the wrist and finger extensors. Hand function, with the ability to perform a grasp and make a fist, had recovered (Fig 5). There were severe co-contractions among all muscles and also respiratory induced contractions among proximal arm muscles (Table 5.2)

There was perception of touch, proprioception, and vibration in the shoulder and elbow but no sensation in the distal part of the arm or hand and no pseudomotor function in the hand. Touching the ipsilateral, clavicular region was perceived in the hand as wrong way referral of sensation.

Pain was initially located to the entire extremity and treated with 1600mg Gabapentin but without complete resolution of pain. In conjunction with the return of motor function starting approximately 8-10 months after surgery, pain disappeared completely. Electromyography showed good recruitment of normal looking motor units in pectorals, deltoid, triceps, biceps, wrist and finger flexors as well as intrinsic muscles of the hand. There were co-contractions in all muscles and inspiration induced muscle activity in biceps, triceps, deltoid and pectoral muscles (Figure 5.3).

5.5. Discussion

The present study confirms previous reports on recovery of function after spinal cord implantation of avulsed ventral roots in humans. The outcome from re-implantation or reconnection of ventral roots to the ventral spinal cord in cases of complete C5-T1 avulsion injury is comparable to a function gained in cases of a less severe injury with rupture of C5 and C6 spinal nerves and avulsion of C7 to T1 roots. This recovery is, in the more successful cases, connected to muscle synkinesis indicating some extent of inappropriate neuron-muscle contacts. There is alleviation of pain in the recovered part of the arm, but limited sensory regeneration.

Recovery of function after implantation of avulsed ventral roots or conduits of nerve graft to the spinal cord depends on the initial regeneration of new axons from the motoneuron pool of the ventral horn. New axons grow through the white matter of

spinal cord or central nervous tissue, regenerating among CNS glia cells at least for 1mm before reaching the peripheral nervous tissue of the implanted root or peripheral nerve graft. Large motoneuron axons become surrounded by CNS type myelin and at intervals there are CNS type of nodes of Ranvier (Cullheim *et al.*, 1989).By recording intracellularly from motoneurons in the spinal cord and staining individual cells with horseradish peroxidase(HRP) (Cullheim *et al.*, 1989), the functional integration of the regenerated motoneurons in the spinal cord circuits and the trajectories of the new axons could be demonstrated.

Magnetic cortical stimulation demonstrated and verified the clinical observation of connectivity from motor cortex to previously dennervated muscles through the reconstructed spinal cord-peripheral nerve trajectories. The latency of muscle response was generally longer than in the intact arm indicating that the regenerated nerve fibres were not fully developed and less myelinated than on the normal side.

Recovery of muscle power was best in the proximal arm and shoulder muscles. Comparison of the results from patients after complete brachial plexus avulsion and subsequent spinal cord re-implantation with patients after complete brachial plexus injuries but ruptures of upper spinal nerves that were repaired or with the effect of nerve transfers showed no statistical difference (see chapter IV).This means that the most severe, complete, brachial plexus avulsion injury after reimplantation and recovery is comparable in functional outcome to a less severe injury such as rupture of the upper two spinal nerves C5 and C6 and avulsion of C7-T1 where the ruptured spinal nerves were repaired in conventional way.

Regeneration of muscle function after intraspinal repair of a brachial plexus avulsion is influenced and disturbed by co- contractions and muscle synkinesis. There is an obvious lack of neuron –muscle specificity or direction of growth causing aberrant muscle reinnervation. In previous primate studies, a random reinnervation of arm muscles from the normally discrete and topographically arranged populations of motoneurons in the ventral horn of the spinal cord has been demonstrated (Hallin *et al.*, 1999).The somatotopic organisation of motoneurons in the ventral horn had been disturbed. Different functional types of neurons extended processes into the implanted root. As judged by their positions in the ventral horn, neurons that normally innervate trunk muscles or antagonistic muscles such as the triceps participated in reinnervating the biceps. Functionally, this deficient specificity of muscle reinneration was revealed in

experimental animals, clinically as well as electrophysiologically as co-contractions or muscle synkinesis (Hallin *et al.*, 1999). Re-implantation of the avulsed ventral root or a peripheral nerve graft to the spinal cord attracted any motoneuron in the adjacent segment of the ventral horn to extend new axons into the introduced, growth promoting, PNS conduit. As the new axons elongate along the peripheral nerves there is no direction of growth to an appropriate muscle target, thus muscle re-innervation is a more or less random process. It should be noted that the more successful the regeneration the more synkinesis there is, indicating that more motoneurons of various populations in that particular patient have been able to re-grow from the spinal cord.

Lack of specificity of muscle reinnervation from appropriate motoneurons applies also to the recruitment of phrenic nerve cells re-growing into arm muscles causing respiratory related arm muscle contractions, i.e. "the breathing arm". This phenomenon occurred only in the C5 myotome. The "breathing arm" was described by Erb more than a hundred years ago (Swift, 1994). Elbow flexion from respiratory induced arm muscle contractions has been described from regeneration within the PNS in patients who have had nerve transfers after severe brachial plexus injuries, particularly transfers of intercostals nerves (Malessy *et al.*, 1993). The study presented here is the first time "the breathing arm" phenomenon has been described after intraspinal repair of root avulsions caused by CNS regeneration.

The source of this activity is phrenic nerve motoneurons, which are situated in the spinal cord cervical segments at C3, C4 and C5 as discrete nuclei in the most medial part of the ventral horn next to the motoneurons for the shoulder and upper part of the arm. Implantation of a PNS conduit into the ventral part of the spinal cord segment C5 could recruit regeneration from phrenic nerve motoneurons within this segment to elongate to the arm instead of the diaphragm. The "breathing arm" phenomenon in these patients demonstrates spinal cord to peripheral nerve regeneration provoked by this surgery.

In contrast to the successful initial spinal cord regeneration of motor axons is the failure of sensory nerve fibre re-growth into the spinal cord. Elongation of injured dorsal root axons occurs along the PNS segment of the dorsal root but growth is curtailed at the encounter of CNS tissue i.e. astrocytes at the root –spinal cord junction (Carlstedt, 1997). Sensory recovery is therefore poor after this type of surgery where only motor conduits have been reconstructed. Intra spinal afferent sprouting producing terminal fields extending into spinal cord segments that have sustained root avulsion and

deafferentation (McMahon and Kett-White, 1991) could explain such phenomena as referral of sensation from the region of the neck to the hand or vice versa.

A lack of sensory reconnection with pertinent spinal cord segments means lack of muscle proprioception. The inability to activate individual joints that most of these patients experience is the result of a supraspinal led activity without proprioceptive feed back. Muscle functions, in particular purposeful movements without muscle afferents, have been described in rare examples of sensory neuropathy (Cole and Sedgwick, 1992).In their cases, patients could learn to compensate for the loss of perception of muscle function or movements with other sensory qualities such as vision.

The severe pain sustained by patients suffering from brachial plexus avulsion injury is typical(Frazier and Skillern, 1911) and presumed to be caused by the generation of abnormal activity within the dorsal horn of the spinal cord from "deafferentation" of the pertinent spinal cord segments (Ovelmen-levitt, 1988). It was recently described that transfers of nerves to the avulsed brachial plexus could alleviate pain (Berman *et al.*, 1998). Remarkable was the observation that the reduction in pain was correlated to the return of muscle activity rather than other qualities of function (Berman *et al.*, 1998).This concept is certainly supported in the present study where the patient (WH) who recovered muscle activity in all parts of his upper extremity, but very limited sensory function, experienced a complete alleviation of his severe post injury pain when muscle function regenerated. In contrast, other patients such as one who had motor recovery only proximal to the elbow is still suffering from excruciating pain in his hand , where there has been no recovery.

The encouraging demonstration of functional return in the distal part of the arm and hand occurred in one case of a preadolescent patient. Clinical observations of better regeneration of function in children than in adults (Onne, 1962) has been verified electrophysiologically (Hallin *et al.*, 1981).The mechanism behind this difference is largely unknown, but motor axons are known to regenerate faster in young rather than adult animals (Gutman, 1942). A better direction of growth and plasticity has also been suggested to give better function in young individuals.

However, in the present study, patients showed persistent co-contractions and respiratory synkinesis as signs of poor axonal orientation and plasticity but presumably extended regeneration must depend upon a better recruitment of motoneurons to re-grow from the spinal cord.

In conclusion, spinal cord implantation of avulsed ventral roots or reconnection by means of nerve graft is a repair of a spinal cord injury with central nervous regeneration

of function. Shortcomings of the present surgical treatment are poor prognosis proportionate to the delay of surgery, incomplete and unpredictable sensorimotor recovery and loss of motoneurons from the avulsion injury.

Motoneurons die owing to a loss of peripheral target, deprivation of trophic substances from the peripheral nerve and due to vascular trauma leading to glutamate induced excitotoxicity. Re growth of new axons is determined, to a large extent, by processes that occur immediately following injury (Fu and Gordon, 1997). There is a rapid increase in secretion of growth factors by glia cells and from recruited blood borne cells (Brecknell and Fawcett, 1996) as a consequence of the trauma. The biological response to nerve injury emphasises the urgency for nerve repair and therefore the optimal time for surgery is close to the time of injury.

Future possibility for the manipulation and augmentation of the process of spinal cord regeneration and repair in these lesions include novel substances and growth factors. In a recent animal study, a potent neurotrophic substance, glia derived neurotrophic factor (GDNF) and an inhibitor of glutamate release-Riluzole ameliorated but did not normalise motoneuron survival (Bergerot *et al.*, 2004). In combination these substances improved the functional recovery to sub-normal levels regenerating distal function in the paw and toes. This improved recovery appeared to be related to increased dendrite formation, increased motoneoron survival and the neurotrophic actions of GDNF. This combination treatment could offer a new therapeutic strategy to recover distal function in the arm and hand in man after complete brachial plexus avulsion injury.

Chapter VI: Observations of motor phenomena: Co-contraction and the Breathing Arm

6.1. Summary

Co-contraction of a group of limb muscles (agonist and antagonist) or contractions of limb muscles in synchrony with respiration, the "breathing arm" occurs in different neurological conditions such as obstetric or traumatic brachial plexus injury in adult or in people who have cervical nerve roots lesion with or without any surgical intervention for repair (Carlstedt *et al.*, 2004; Holler and Hopf, 1968; Swift *et al.*, 1980). These phenomena were noted in 70% of patients in this study. In 3 patients, the source of the breathing arm was from re-implantation. In a recent study by (Carlstedt *et al.*, 2000) concluded that this could be due to aberrant muscle re-innervation from the re-implanted nerve. In repair of the rupture nerve, the clinical phenomenon of co-contraction could be simply due to misrouting of regenerated nerve fibres (Crumley, 1979; Guerrissi, 1991) In the cases of re-implantation, the injury and the repair sites were within the spinal cord. Synkinesis could result from several axons being produced by the same motor neuron i.e. supernumerary axons (Havton and Kellerth, 1987) , non directional regeneration or lack of muscle afferents. There was a similar recovery pattern between patients with and without "breathing arm'' although strong co-contraction of agonist and antagonist muscles hampered functional recovery despite good regeneration. In patients for whom nerve grafts were implanted directly into the C5 spinal cord segment, the "breathing arm" demonstrated regeneration within the spinal cord i.e. CNS to PNS regeneration, and in other cases primarily PNS regeneration. There is limited motor plasticity during the process of recovery.

6.2. Introduction

It is known that cross-reinnervation occurs when regenerating nerve fibres recombine after brachial plexus injury and causes abnormal contraction in many muscles simultaneously i.e. synkinesis during voluntary movement(Roth, 1983; Yagi, 1984). Synkinesis is found mainly in the pathology of cranial nerves especially the facial nerve (Valls-Sole and Montero, 2003) and observation of this phenomenon in limb muscles remains uncommon. Co-contraction after brachial plexus injuriy is different from co-ordinated movements of a group of muscles contracting. For example, normally, during movement a group of muscles contracts simultaneously in co-ordinated fashion with the same purpose but co-contraction after brachial plexus injury is in fact, contraction of

different muscle groups, in particular agonist and antagonist. This can hamper the functional recovery even though individual muscles are well reinnervated (Benaim *et al.*, 1999; Magalon *et al.*, 1981; Magalon *et al.*, 1982).Synkinesis can be observed among limb muscles but it can also be seen between limb muscles and respiratory muscles. Some patients who have brachial plexus injuries are showing the unusual phenomenon of the "breathing arm". This refers to contractions of arm muscles synchronous with respiration. It can be seen in different neurological conditions such as adult traumatic or obstetric brachial plexus injury or in people who have lesions of cervical nerve roots with or without any surgical intervention for repair (Holler and Hopf, 1968; Swift *et al.*, 1980).

This "breathing arm" phenomenon has been described in patients who have had a variety of operations for repair of brachial plexus and especially after intercostal nerve transfer (Malessy *et al.*, 1993; Takahashi, 1983). Synkinesis between respiratory muscles and arm muscles can be observed either clinically or by EMG examination. The phenomenon was described by Erb more than a hundred years ago (Swift, 1994) and by others more recently (Holler and Hopf, 1968; Kawai, 1993; Kawanishi and al, 1992; Robinson, 1951; Sakai *et al.*, 1991; Schwarz, 1965). Respiratory induced contraction of the biceps muscles can be observed clinically in some patients. Muscle activity can be sometimes seen as rippling under the skin or the arm may move in association with breathing. On needle EMG examination, motor units can be seen to fire synchronously with respiration. These respiration related activities can be seen either on inspiration or expiration or both phases of respiration and also when coughing (Chuang *et al.*, 1992; Robinson, 1951; Sibuya *et al.*, 1987; Swift, 1994; Takahashi, 1983). The muscle unit potentials (MUP) associated with respiration have been reported to be present as early as 4 to 8 months after trauma or surgery and then to fade away gradually (Takahashi, 1983). However, involuntary muscle contraction of the biceps still occurred when the patient sneezed or coughed (Nagano *et al.*, 1989). In other studies, particularly in patients with obstetric brachial plexus palsy, muscle contraction associated with respiration was still present 20 years later (Robinson, 1951; Schwarz, 1965).

Usually the "breathing arm'' is described in patients with brachial plexus injury after intercostal nerve transfer to the musculocutaneous nerve (Malessy and Thomeer, 1998; Takahashi, 1983). But reports on the occurrence of "breathing arm'' phenomenon after repair of proximal brachial plexus injuries are rare. This phenomenon occurs after proximal brachial plexus lesion as the phrenic nerve is connected to the 5^{th} cervical

spinal nerve root, which usually is the most rostral spinal nerve root to the brachial plexus innervating proximal arm muscles. Thus, injury to the 5th cervical nerve could lead easily to aberrant re-growth of phrenic axons into arm muscles instead of the diaphragm. No such cases have been reported after intra-spinal cord repair. In this study, the "breathing arm'' was assessed in patients with brachial plexus injuries after various extra and intra spinal reconstructions and the underlying mechanisms of this phenomenon explored. The presence of the "breathing arm'' in patients who have had repair of the most proximal brachial plexus lesions and the relation to central to peripheral regeneration is discussed.

6.3. Methods

Thirty seven patients out of forty one patients who had surgical repair were studied for motor recovery and assessed (refer to Chapter IV) for the presence of ''breathing arm'' and limb muscle co-contraction.

All patients underwent a detailed neurological examination. Motor power in the upper limb was assessed using the grading recommended by the Medical Research Council.

After the repair of spinal nerve root injury, co-contraction of a group of limb muscles (agonist and antagonist) and rhythmic contraction of the limb muscle was examined clinically when possible and recorded by EMG machine.

Please refer to the Previous Chapter III for methods.

Statistics: The data was analysed statistically using Mann-Whitney U test and Kruskal-Wallis statistic. *P*-values <0.05 were considered to be significant. Data are presented as mean ± SEM (standard error of mean) if otherwise stated. (Refer to Chapter III).

6.4. Results

6.4.1. Clinical: The "breathing arm" and limb muscle co-contraction

Muscles normally innervated from C5 and C6 spinal cord segments showed respiratory synkinesis (pectoral, deltoid, biceps and triceps muscles) (Figure 6.1). Co-contraction among different muscles was observed also on volitional limb movement (Figure 6.2) and breathing arm was shown in (Figure 6.3). However, these did not always co-contract with in synchrony with breathing. In four patients ((DH, BP, PH, TH) co-contractions between biceps and triceps upon voluntary effort was observed, but the breathing- related muscle activity appeared only in the biceps muscle. As can be seen in Table 6.1, twenty five out of thirty seven patients were found to have both "breathing

arm" and co-contraction whilst nine patients showed no evidence of the "breathing arm" but had limb muscle co-contractions. One patient showed evidence of the "breathing arm" but not co-contractions. Two patients had neither the "breathing arm" nor co-contractions. In three out of twenty six patients, the source of "breathing arm" could only have been from re-implanted ventral roots as there is no other possible way or regeneration of the muscles apart from re-implantation whilst one patient, repaired by re-implantation showed co-contraction but no "breathing arm". In the remaining patients, the source of the "breathing arm" could be from C5 nerves, intercostal nerves or the accessory phrenic nerve.

Table 6.1. The source of "breathing arm".

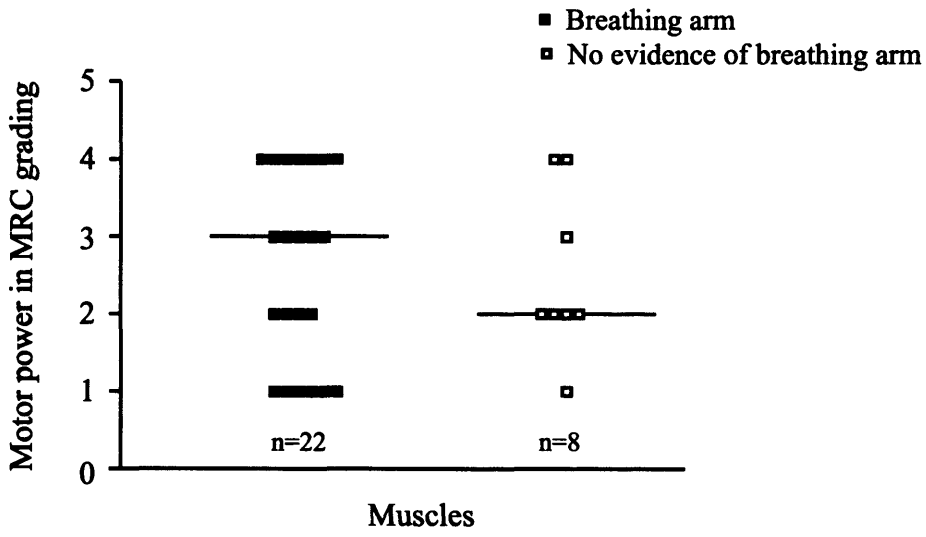
	Number of Patients
Breathing arm and co-contraction	25*
Breathing arm only	1
Co-contraction only	9
No breathing arm or co-contraction	2
Total	**37**

*In 3 patients, the source of breathing arm was from re-implantation.

In general, muscle activity synchronous with and elicited by breathing was found in muscles with some recovery of volitional function. Breathing-related muscle contractions were found mainly during inspiration, and occasionally during forceful expiration and coughing. Muscle contractions elicited by respiratory activity did not result in any clinically meaningful movements and were therefore of no functional importance.

The power of the biceps muscle (Mean ± SEM) in patients with and without the "breathing arm" was 2.6 ± 0.3 and 2.5 ± 0.4 respectively (Figure 5.1) and showed no statistically significant difference (p=0.9).

Figure 6.1. Motor power of the biceps muscle in patients with or <u>without</u> "breathing arm".



Mean values (± SEM) for the duration after injury for patients with or without the "breathing arm" was 6.7 ± 1.5 and 5.2 ± 1.5 years respectively and showed no statistically significant difference (p=1.0). The "breathing arm" phenomenon was detected from as early as 1.1 years and up to 19 years after injury.

6.4.2. Neurophysiological studies

EMG examination

EMG examination of affected muscles generally showed evidence of partial denervation with re-innervation. Motor unit potentials (MUPs) firing synchronously with respiration (inspiration) in quiet or voluntary breathing were observed in several cases. The same motor units could usually be activated by volitional contraction. MUPs firing simultaneously were observed in groups of muscles including agonist and antagonist muscles which were seen to co-contract. Examples of these observations are shown in Figures 6.2 and 6.3.

Figure 6.2. Electromyography studies: Multichannel EMG recording of co-contracting muscles in the injured upper limb, traces of motor unit potentials (MUPs) firing during voluntary contraction.

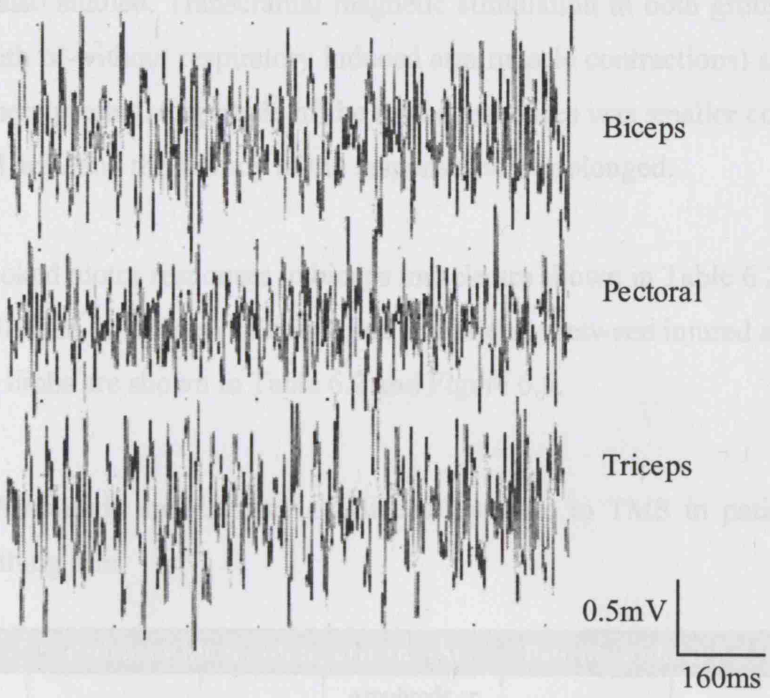
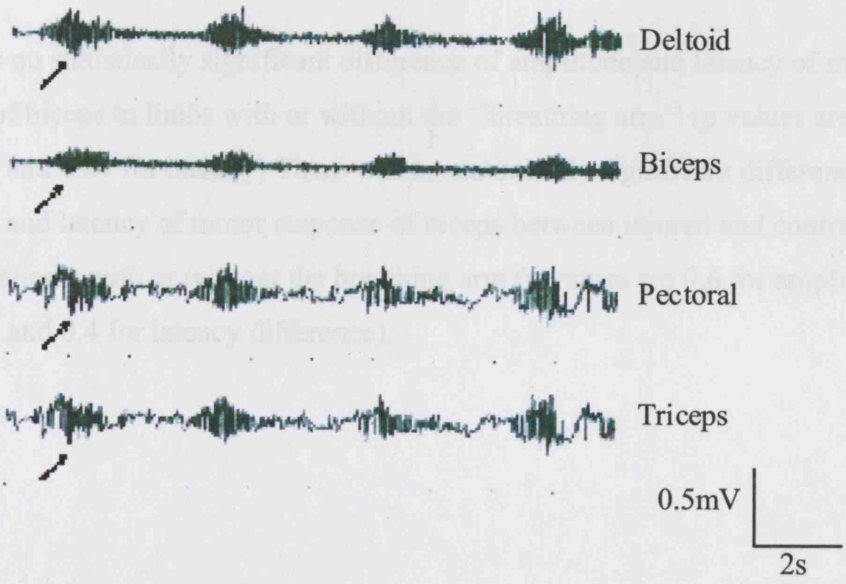


Figure 6.3. Electromyography studies: Multichannel EMG recording of muscles in the injured upper limb showing bursts of motor units firing synchronously with inspiration, and traces of motor unit potentials (MUPs) were firing in breathing.



Transcranial Magnetic Stimulation (TMS)

The TMS evoked motor responses in biceps muscles with and without the "breathing Arm" were also studied. Transcranial magnetic stimulation in both groups of patients, (i.e. those with or without respiratory induced arm muscle contractions) showed similar findings. Where present, amplitude of the motor responses was smaller compared to the contra lateral arm, and the latency of the responses was prolonged.

The TMS evoked motor responses in biceps muscle are shown in Table 6.2 and Figure 6.4A and 6.4B.The differences of amplitude and latency between injured and contralateral limbs are shown in Table 6.2 and Figure 6.5.

Table 6.2. Amplitude and Latency of Biceps response to TMS in patients with and without breathing arm.

	Patients with breathing arm (n=18)			Patients without breathing arm (n=5)		
	Contra lateral	Injured	Amplitude or Latency differences (mV or ms)	Contra lateral	Injured	Amplitude or Latency differences (mV or ms)
Amplitude (mV)	4.9 ± 1.0	1.4± 0.3	3.5 ± 1.0	3.8±1.4	1.5±0.3	2.3 ± 1.6
Latency (ms)	11.6 ± 1.3	17.6± 1.3	6.0 ± 1.2	9.3±1.3	13.3±1.9	4.0 ± 1.8

Values are mean ± SEM.

There was no statistically significant difference of amplitude and latency of motor response of biceps in limbs with or without the ''breathing arm'' (p values are 0.5 for amplitude and 0.07 for latency) There was no statistically significant difference of amplitude and latency of motor response of biceps between injured and contralateral limbs in patients with or without the breathing arm (p values are 0.6 for amplitude difference and 0.4 for latency difference).

Figure. 6.4A. Amplitude of motor response of biceps in patients with and without breathing arm.

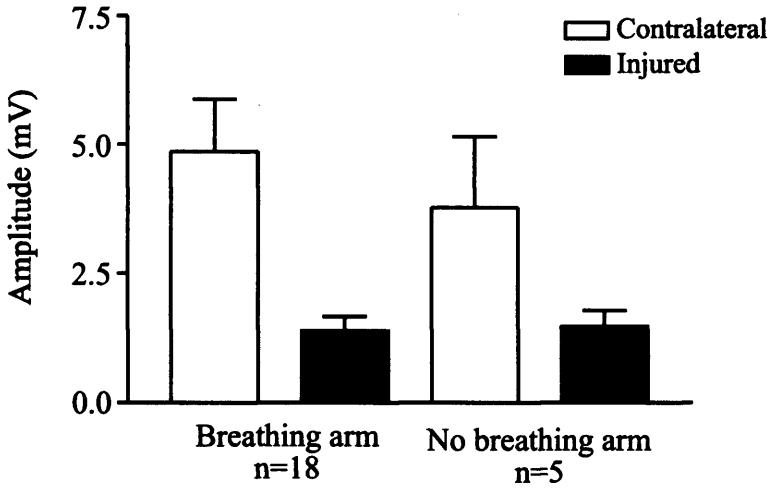


Figure 6.4B. Latency of motor response of biceps in patients with and without breathing arm.

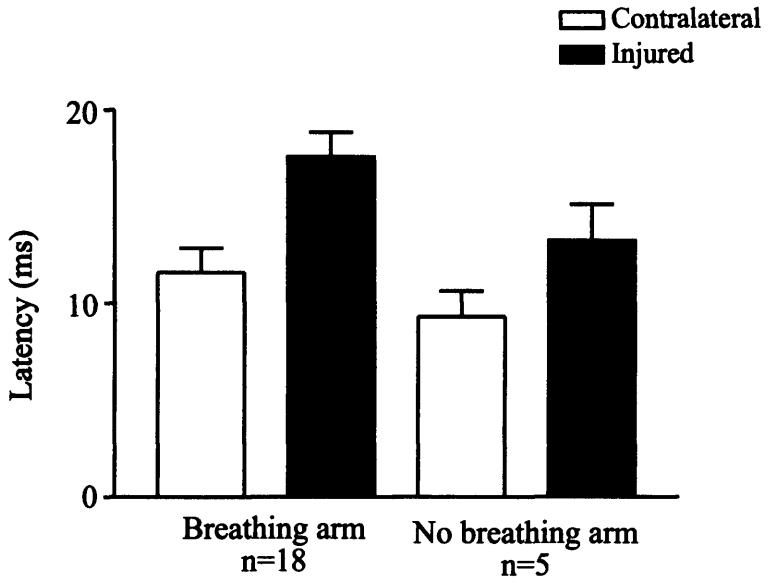
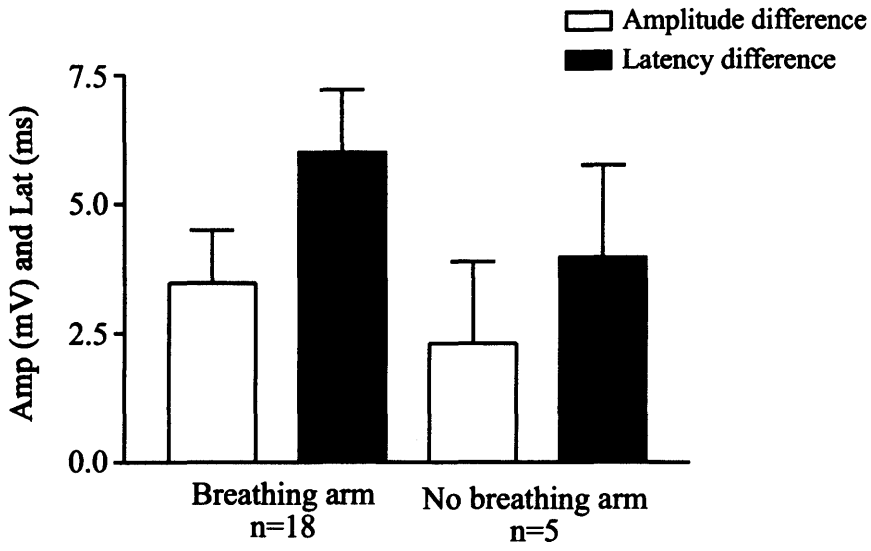


Table 6.3. Amplitude and Latency Differences of biceps. Motor Evoked response of contralateral (non injured side) and injured side of patients with breathing arm and patients without breathing arm.

	Patients with breathing arm (n=18)		Patients without breathing arm (n=5)	
	Amplitude difference	Latency difference	Amplitude difference	Latency difference
Mean	3.5 ± 1.0	6.0 ± 1.2	2.3 ± 1.6	4.0 ± 1.8

There was no statistically significant difference of amplitude or latency of motor response of biceps between injured and contralateral limbs in patients with or without the breathing arm ($p = 0.6$ and 0.4 respectively).

Figure 6.5. Amplitude and latency differences of motor response of biceps in contra-lateral and injured side in patients with "breathing arm" and patients without "breathing arm".



6.4.3. Illustrative Cases

The salient features of pairs of patients repaired by different methods are given below. For each pair of patients the similar repair method has been used but one patient from each pair showed evidence of 'the breathing arm'.

***Replantation*:**

JJ (D.O.B: 8.9.71) - with "breathing arm"

This patient suffered a right brachial plexus injury at the age of 28 years as a result of a motorcycle accident. C5, C6, C7, C8 and T1 nerve roots were avulsed. The ventral root of C6 was also ruptured with a proximal stump remaining in continuity with the spinal cord. The C5 and C7 nerve roots were re-implanted and one graft was connected to the ventral root stump of C6. The patient was assessed 3 years later. Motor power (MRC grading) on the injured side was as follows: serratus anterior was 3, pectoralis majors 4, latissimus dorsi 2, deltoid 0, biceps 3, triceps 3 and the remaining forearm and hand muscles were 0. Clinically, there was obvious co-contraction of the biceps, triceps and pectorals muscles. There were visible contractions of the pectorals and possibly the biceps during inspiration.

On needle EMG examination, sparse fibrillations were recorded from the deltoid and triceps. Polyphasic, single, discrete motor units were recorded from the deltoid while more abundant motor units could be recruited from the biceps, triceps and pectorals. The biceps, triceps and pectorals showed co-contraction with any voluntary movement of the arm. All of these muscles (including deltoid) showed motor unit activity synchronised with inspiration.

Transcranial magnetic stimulation of the brain evoked motor responses from the right pectoral and biceps muscles. The amplitudes of the responses were smaller than on the opposite side and had slightly longer latencies.

Comment: In this patient, the breathing arm must originate from re-implantation of the C5 and C6 roots into the spinal cord. Although there was no clinically detectable power in the deltoid, there was clear EMG evidence of that it was re-innervated and indeed there is also EMG evidence of "breathing arm".

MB (D.O.B: 8.2.69) - without "breathing arm"

This 30 year old patient suffered a right brachial plexus injury as a result of a motorcycle accident. C5, C6 and C7 nerve roots were avulsed and C8 and T1 nerve roots were ruptured. Repair involved re-implantation of C5, C6 and C7 whilst C8 and T1 were grafted. The patient was assessed approximately 2 years after the injury. Motor power (MRC grading) of serratus anterior was 3, pectoralis majors 4, latissimus dorsi 3, deltoid 0, biceps 2, triceps 3 and the remaining forearm and hand muscles were 0 on the injured side. There was no obvious clinically detected co-contraction of pectorals, biceps and triceps.

Needle EMG examination revealed signs of chronic partial denervation with re-innervation in the pectorals, biceps, and triceps. There was co- contraction between the pectorals and triceps on volitional effort. No motor unit activity was seen in relationship to breathing or coughing.

TMS of the brain evoked motor responses from the pectorals and triceps, which were recorded with smaller amplitudes and slightly longer latencies than on the contralateral side.

Reconstruction of ruptured spinal nerves with nerve grafts:

Mo B (DOB: 1.5.79) - with "breathing arm"

This patient suffered a left brachial plexus injury 21 years of age as a result of a motorcycle accident. He had rupture nerve roots at C5 and C6 and avulsed those at C7, C8 andT1 nerve roots. The upper trunk was grafted to C5 and C6 and the avulsed C7 was grafted to proximal stump. The accessory nerve was transferred to the ventral root of the avulsed C8 root. He was studied approximately 2 years following injury. The motor powers (MRC grading) of the serratus anterior, pectoral, latissimus dorsi, biceps and triceps were 4 and spinatii and deltoid were 1 on the injured side. Clinically, there were obvious co-contractions of pectorals, biceps and triceps.

On Needle EMG examination there were signs of chronic, partial denervation with re-innervation in the biceps, and triceps along with co- contraction between pectorals and triceps on volitional effort. There was also evidence of motor units firing in synchrony with respiration in biceps and triceps.

Trans-cranial magnetic stimulation of the brain evoked motor responses from the left pectoral and triceps. The amplitudes of the responses were smaller than on the opposite side and slightly longer in latency.

Comment: The "breathing arm" activity may originate from phrenic nerve motor neurones through the nerve graft rather than from the accessory phrenic nerve to C8.

RS (D.O.B: 2.9.72) - without "breathing arm"

This patient suffered a left brachial plexus injury following a motorcycle accident at the age of 27 years. He had proximal rupture of nerve root at C5 and avulsion of nerve roots at C6 and C7, lesion in continuity of C8 and intact T1.Repair was done by means of graft from C5 nerve root to ventral roots of avulsed C6 and C7, transfer of intercostals nerves T4 and T5 to the musculocutaneous nerve and T3 to the long thoracic nerve. In

addition, assessory nerve was transferred to the suprascapular nerve. He was studied approximately 3 years after injury. The motor powers (MRC grading) of his serratus anterior was 5, pectorals 4,deltoid 4, biceps 2, triceps 4, brachioradialis 3, ECRL 4 and wrist and finger extensors as well as flexors were 5. There were clinically obvious co-contractions among pectorals, biceps and triceps.

Needle EMG examination showed signs of chronic partial denervation with re-innervation in the pectorals, biceps, and triceps and motor units also firing in his biceps on attempting to bend or straighten his elbow i.e. co-contraction of biceps and triceps on volitional effort. No motor unit activity was detected in relationship to breathing in pectorals, biceps and triceps in needle EMG examination.

Trans-cranial magnetic stimulation of the brain evoked motor responses from the left pectoral, biceps and triceps. The amplitudes of the responses were generally smaller than on the opposite side and slightly longer in latency.

Nerve transfers:

PC (D.O.B: 21.4.77) - with "breathing arm"

The patient had a right brachial plexus injury at 23 years of age following a motorcycle accident.

There were nerve roots ruptures at C5, C7 and C8 and avulsion at C6 and T1nerve roots. Reconstruction was achieved by means of nerve grafts from proximal stumps at C5 and C8 nerve roots to the upper trunk and ventral root of avulsed C8. An accessory phrenic nerve was sectioned and joined to the ventral root of avulsed C6.He was assessed approximately 2 years after injury. Motor power (MRC grading) for deltoid, pectoral, latissimus dorsi, serratuus ant, spinati and teres major muscles was 4,biceps and triceps muscle was 2 and the remaining forearm and hand muscle were 0.Other clinical observations included co-contraction of biceps, triceps and pectorals and contraction of biceps synchronously with inspiration.

Needle EMG examination of biceps and triceps showed signs of chronic partial denervation with re-innervation and in the biceps, motor units were firing in synchrony with inspiration. No motor unit activity seen in relationship to breathing in triceps.

TMS of the brain evoked motor responses from the right biceps and triceps. Amplitudes of the responses were smaller than the contralateral side with slightly longer latency.

Comment: In this case, the origin of "breathing arm" activity is obvious and clearly due to the accessory phrenic nerve to C6 nerve root transfer.

Patient without repair but has "breathing arm"

PK (D.O.B: 1.9.1962)

This patient had a left brachial plexus injury at 17 years of age. His brachial plexus was explored. There were avulsions of nerve roots of C5, C6 and C7. Exploration of nerve roots of C8 and T1 was impossible because of dense scarring. No attempt was made to repair his plexus. He was assessed 22 years after injury and showed very poor or negligible recovery. Motor power (MRC grading) of his serratus anterior was 4 and the rest of injured upper limb is 0. Needle EMG examination of the pectorals showed evidence of chronic partial denervation with re-innervation and motor units firing synchronously with inspiration.

Comment: Though there was a response from the intact phrenic nerve on stimulation, there was no distal muscular response suggesting that the phrenic nerve might have been damaged to some extent but not avulsed. It would be reasonable to suggest that the likely source of the "breathing arm" would be misrouting of the regenerated phrenic nerve to the nerve supplying the pectorals (Swift, 1994).

6.5. Discussion

Co-contraction

Although there was a similar functional recovery in patients repaired by different surgical methods(please refer to previous chapter), recovery was often hampered by muscle co-contraction despite re-generation (Carlstedt *et al.*, 2004). Co-contractions between agonist and antagonist arm muscles on voluntary movement was seen in 34 out of 45 patients. This could be due to aberrant muscle re-innervation (Carlstedt *et al.*, 2000). Following repair of the ruptured nerve, the clinical phenomenon of co-contraction could be simply due to misrouting of regenerated nerve fibres (Crumley, 1979; Guerrissi, 1991). In cases of re-implantation, the injury and repair sites are within the spinal cord, synkinesis could result from several supernumerary axons being produced by the same motor neurons (Havton and Kellerth, 1987). Studies in primate showed a random reinnervation of arm muscles from the normally discrete and topographically arranged populations of motor neurons (Hallin *et al.*, 1999).The motorneurons which regrew in the implanted roots were from various nuclei in the spinal cord. Different functional pools of motoneurons were attracted to regrow axons on the implanted root, as judged by their position in the ventral horn and therefore neurons, which normally supplying an antagonist muscle, such as the triceps participated in the innervation of the biceps muscle, manifesting in co-contraction of

agonist and antagonist muscles (Carlstedt *et al.*, 2000). Alternatively, this phenomenon may be simply due to the absence of the Ia fibres which are responsible for reciprocal inhibition. However, co-contraction was usually observed in more than two muscle pairs (agonist and antagonist) for example, when the biceps contracted, other muscles such as pectorals, deltoid triceps and even forearm muscles contracted synchronously. These findings are consistent with unselective reinnervation rather then a failure of Ia fibres to regenerate.

"Breathing arm"

In some patients with brachial plexus injury, the limb and trunk muscles, which are not normally involved in breathing, acquired some breathing related functional properties through aberrant regeneration. This is in fact co-contraction of limb muscles and muscles responsible for breathing.

Normally, the diaphragm, intercostal, parasternals, scalenes and abdominal muscles normally perform respiratory motor function. The diaphragm is the most important inspiratory muscle accounting for 70% of tidal ventilation (Decramer, 1998). Other inspiratory muscles are external intercostal, parasternal, and scalene. The internal intercostal and abdominal muscles are involved in expiration, coughing and sneezing (Decramer, 1998).

The diaphragm is innervated by the phrenic nerve which is derived chiefly from the 4^{th} cervical nerve, with contributions from the 5^{th} cervical nerve and sometimes from the 3^{rd} cervical nerve. One third of the population also has an accessory phrenic nerve, usually derived from the 5^{th} cervical nerve which runs a variable course in the thorax and also innervates the diaphragm (Bunge, 1993; Gray and Williams, 1989; Zhang *et al.*, 2004). The intercostal muscles are supplied by intercostals nerves (Bunge, 1993; Swift, 1994). Phrenic and intercostals nerves are classified as spinal nerves and controlled via the descending lateral corticospinal tract of the spinal cord (Gray and Williams, 1989).

Needle EMG examination of the limb muscles in "breathing arm" have shown the MUPs with patterns characteristic of diaphragm (Swift, 1994). Fluoroscopic studies of the movement of the diaphragm and limb muscles in "the breathing arm" showed synchronous contraction (Robinson, 1951).This phenomenon occurs after proximal brachial plexus lesion. The phrenic nerve is closely related with the 5^{th} cervical spinal

nerve root. The 5th spinal nerve is usually the most rostral spinal root nerve to the brachial plexus innervating proximal arm muscles. Injury to the 5th cervical nerve could therefore easily lead to aberrant re-growth of phrenic axons to arm muscles instead of the diaphragm. "Breathing arm" is usually reported in patients following transfer of intercostals nerve to musculocutaneous nerve (Malessy and Thomeer, 1998; Takahashi, 1983) whilst reports of its occurrence after repair of proximal brachial plexus injuries are rare. In our patients showing "the breathing arm" phenomenon there was evidence of motor activity in limb muscles associated with involuntary and voluntary breathing and coughing. For those who had repair of the upper trunk, the sources of "breathing arm" presumably came from the phrenic nerve motor neurones, which are situated in the spinal cord at cervical 3, 4 and 5 segments. In addition, fibres that contribute to the phrenic nerve sometimes travel via the C5 nerve before joining the phrenic nerve (Zhang *et al.*, 2004). Injuries to the upper trunk and subsequent regeneration could lead to synkinesis between muscles of the limb and diaphragm (Schwarz, 1965; Swift, 1994). It would be reasonable to assume that the source of "breathing arm" in patients with lower plexus injury repaired by intercostal nerve transfer is through a similar mechanism.

In those patients with re-implantation, the source of "the breathing arm" activity is directly from regeneration within the spinal cord segment. The phrenic nerve motoneuron is discrete and situated in the most medial part of the ventral horn adjacent to the motoneurons supplying the shoulder and upper part of the arm. Evidence from animal experiments has shown that structural changes of phrenic nerve neurons occur after spinal cord lesion and suggest that there is an "unmasking" of their synapses. Gosharian *et al* discovered that specific morphological changes in the normal ultrastructure of the rat phrenic nucleus occurred within 4 hours after an ipsilateral spinal cord hemisection rostral to the nucleus. There was a significant increase in the number of double synapses which remained significantly higher than normal at all other posthemisection periods. A significant increase in the length of dendrodendritic membrane appositions was also noted (Goshgarian *et al.*, 1989; Sperry and Goshgarian, 1993) . Implantation of a peripheral nervous system conduit into the ventral part of the C5 spinal cord segment could allow for regeneration of the phrenic nerve motorneurons within this segment, thereby innervating the arm instead of the diaphragm (Carlstedt *et al.*, 2004)

Several studies, including those in animals, have shown spontaneous motor unit activity in the biceps brachi muscle which was synchronised with respiration in the early stages

of reinnervation. This involuntary element disappeared gradually as volitional control and endurance improved (Chuang *et al.*, 1992; Friedman *et al.*, 1990; Isla *et al.*, 1999; Nagano *et al.*, 1989; Narakas and Hentz, 1988; Takahashi, 1983). Plastic changes in the nervous system at different levels from the cortex to target muscles after neurotization and brachial plexus injury in patients and animals have been shown in several studies (Iwase *et al.*, 2001; Kanamaru *et al.*, 1999; Kawanishi and al, 1992; Malessy *et al.*, 2003; Malessy *et al.*, 1998a; Malessy *et al.*, 1998b; Mano *et al.*, 1995; Wolpaw, 2001; Zhang *et al.*, 2004). However, this study confirms and extends other reports which documented that the "breathing arm" phenomenon persists for many years after injury (Holler and Hopf, 1968; Robinson, 1951) This is further reinforced phenomenon with studies in animals. In adult mammals, there is an inability of motor programs to change when innervating a new target and the original motor circuits are maintained even when motorneurons innervates a foreign muscle (Gruart *et al.*, 2003).

Our patients with or without the "breathing arm" had similar brachial plexus lesions and underwent similar repair operations. Recovery of motor function clinically as well as electrophysiologically in both groups shared a similar trend and thus suggests that the role of motor plasticity play only limited role except cases associated with severe co-contraction of agonist and antagonist muscles which could be helped by some re training of affected muscles group (Cronin and Steenerson, 2003; Nakamura *et al.*, 2003).

Conclusions:

In patients in whom nerve grafts were implanted directly into the C5 spinal cord segment, the "breathing arm" demonstrates regeneration within the spinal cord i.e. CNS to PNS regeneration, and in other cases primarily PNS regeneration. Though there is motor plasticity during the process of recovery this has a limited role for functional recovery.

Chapter VII: Recovery of sensory functions and referred sensations after surgical repair of brachial plexus injury

7.1. Summary

Seventy six patients with severe brachial plexus avulsion injuries, repaired by different surgical techniques, were studied for sensory recovery and referred sensations using quantitative sensory testing. After repeated testing over an average follow-up period of two years, sensory recovery was observed most consistently in C5 dermatome in response to warm and cool stimuli. Referred sensation were designated as "right-way" if referred to the original source of the afferents, and "wrong-way" or other if not (e.g. referral of sensation down the affected arm whilst shaving the face). Right-way referral of sensation occurred at a later stage of recovery (> 6 months, 11.8% of cases), and appeared to be related to peripheral nerve regeneration with a Tinel's sign, whereas wrong-way referral (43.4% of the cases) sometimes occurred earlier, often accompanied with unusual phenomena (e.g. referral of sensation down the affected arm when drinking cold fluids), suggesting CNS plasticity. This study concluded that, due to the complexity of the sensory system, recovery of sensory function depends not only on technically successful nerve repair but also on CNS plasticity.

7.2. Introduction

Injuries to the brachial plexus may lead to spinal nerve rupture outside the intervertebral foramina or proximal to this site, either as an intraspinal rupture or as root avulsion from the spinal cord. Root avulsions occur particularly in brachial plexus traction injury and affect spinal cord circuits leading to monoplegia. There may also be an associated Brown-Sequard syndrome due to additional spinal cord injury. Root avulsions usually involve both the ventral and dorsal roots of spinal nerves and the patient suffers from paralysis and sensory dysfunction which manifests as numbness of the limb often in conjunction with extreme, intractable pain (Berman *et al.*, 1998; Birch, 1998; Wynn Parry, 1980).

The function of the sensory nervous system in most living organisms is not merely to sense and monitor the environment but also essential for the survival. Hence impaired sensory function has grave consequences. After traumatic brachial plexus injury, patients usually lose somatic sensation as well as motor and autonomic functions. The somatosensory system has a peripheral and a central nervous part. Peripheral nerve

fibres carry messages transmitted from sensory receptors and enter the central nervous system, the spinal cord, via the dorsal roots. In the spinal cord the sensory message travels via ascending lateral spinal thalamic tracts and dorsal columns and eventually reaches the sensory cortex (the parietal cortex). There are three different cutaneous sensory receptors: mechanoreceptors, thermoreceptors and nociceptors (Brown William *et al.*, 2002). Vibration is registered by both cutaneous sensory receptors and sensory receptors in deeper somatic structures (proprioceptors) (Ropper Allan *et al.*, 2001). Different sensory impulses are mediated by different fibre types within the peripheral nerves. Sensations of touch, vibration and proprioception are carried by large myelinated A-α fibres whilst myelinated small A-δ fibres carry sensations of cold and pain. Unmyelinated, small fibres carry the warm sensation. Proprioceptic receptors are located in the deeper structures such as muscles, tendons and ligaments. In the spinal cord, primary afferents relay sensory information to second – order sensory neurons, most of which lie in the dorsal horn of the spinal cord (Bear Mark *et al.*, 2001) but also in the upper part of the spinal cord,the gracile and cuneate nuclei. Sensory afferent fibres travel are arranged in the ascending spinal cord tracts and further as the medial lemniscus which travels via the medulla, pons and mid brain to synapse in the ventral posterior (VP) nucleus of the thalamus. From there sensory information reaches the sensory cortex which is somatotopically organised (Bear Mark *et al.*, 2001; Penfield Wilder and Rasmussen, 1950).

In some patients, sensory stimulation (thermal and mechanical) of the avulsed dermatome has been reported to be perceived abnormally, or experienced at remote sites with or without phantom sensations. This is thought to be related to reorganisation of the somatosensory system following deafferentation (Condes-Lara *et al.*, 2000; Flor *et al.*, 1995; Flor *et al.*, 2000; Kaas, 2000; Malin and Winkelmuller, 1985; Moore *et al.*, 2000; Ramachandran and Hirstein, 1998).

In this study, the recovery of different somatic sensory modalities; tactile sensation, vibration and temperature sensation after traction brachial plexus injury using quantitative sensory testing has been assessed. The different presentations of sensory phenomena i.e. referred sensations have been also examined.

In this study phantom sensation is defined as any spontaneous sensation of the deafferented part of body. Referred sensation (RS) is defined as any sensation evoked by any stimuli outside the deafferentated part of body. However, these terminologies

have been used interchangeably in other studies (Grusser et al., 2004; Ramachandran, 1993; Ramachandran and Hirstein, 1998).

7.3. Methods

7.3.1. Patients

Seventy six patients who had sustained brachial plexus injury were studied after the patients and local ethics committee approval. All patients gave their informed consent. Patients had been referred to the Peripheral Nerve Injury Unit, Royal National Orthopaedic Hospital, London, UK. Clinical assessments and neurophysiological studies were performed at the Hammersmith Hospital, London, UK.

Patients with associated spinal cord or brain injury, injury to proximal major blood vessels, or double level lesions were excluded. Avulsion or intra-spinal injury was confirmed by computerised tomography (CT)-myelography, per-operative electrophysiology, and direct intra-operative inspection of the exposed brachial plexus and spinal cord (if applicable). Spinal nerves were either ruptured outside the intervertebral foramina or lesioned proximal to this site either as intraspinal rupture or root avulsion from the spinal cord. Ruptured spinal nerves were subjected to nerve grafting. In cases of root ruptures or avulsion from the spinal cord, root re implantation into the spinal cord (Carlstedt *et al.*, 2000; Carlstedt *et al.*, 1995) or nerve transfers were performed. **Details of the severity of the lesion and methods of repair are described in the next Chapter (VIII).**

The mean age of patients at the time of injury was 28.4 ± 1.1 years and the mean time of assessment was 4 ± 0.5 years after the injury. The earliest assessment was 4 days post-injury and the latest assessment was made after 40. 6 years.

For patients who were assessed twice (n=9), a baseline study was performed 14 ± 7 weeks (minimum 8 weeks and maximum 28 weeks) after injury. A second assessment was conducted at 2 years ± 6 months (minimum 11 months and maximum 5 years) after injury. The time interval between base line and second assessment was 2 years ± 6 months (minimum 10 months and maximum 5 years).

7.3.2. Sensory tests

Details of sensory testing, including quantitative sensory tests are discussed in the previous Chapter III. The method of observation of "referred sensations" is also given in Chapter III.

Statistics : The Mann-Whitney U and Kruskal-Wallis tests were used. *P*-values <0.05 were considered to be significant. Data are presented as mean ± SEM (standard error of mean) unless otherwise stated. (Refer to Chapter III for details.)

7.4. Results

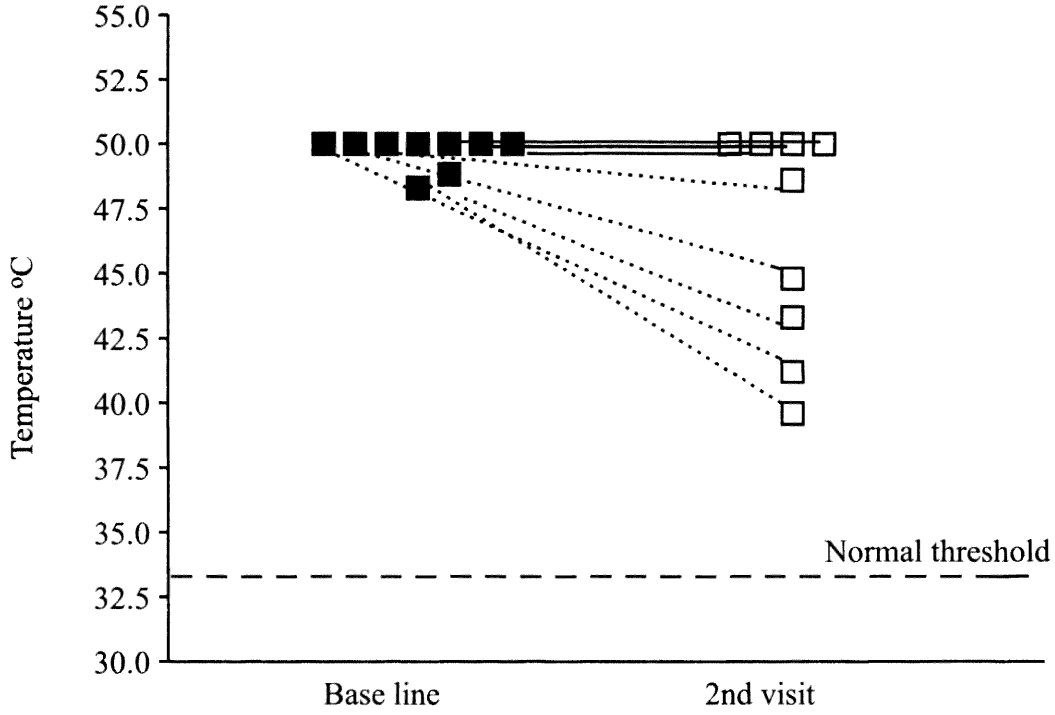
7.4.1. Sensory recovery

Different sensory modalities in affected dermatomes showed very poor or no recovery. The best recovery was found in C5 dermatome in some of the patients (n=9). (Table 7. 1 and Fig. 7.1 and Fig. 7. 2)

Table 7.1. Sensory recovery at C5 dermatome.

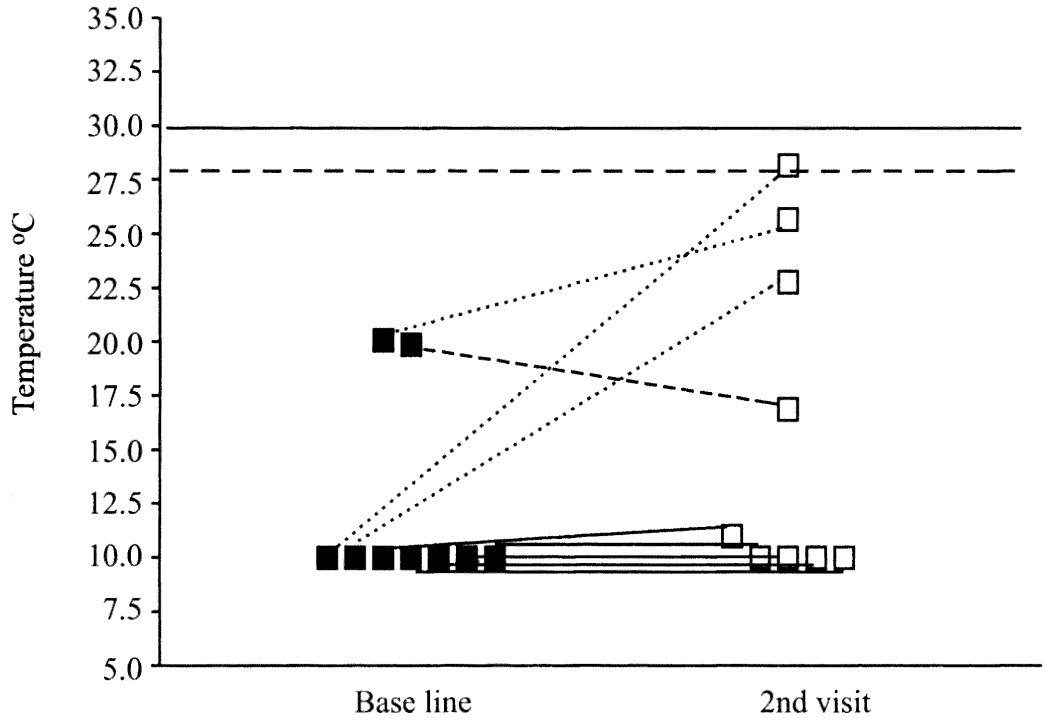
	Monofilament (Number)			Cool threshold (°C)			Warm threshold (°C)		
	Mean ±SEM	Max	Min	Mean ±SEM	Max	Min	Mean ±SEM	Max	Min
Base line assessment	14 ± 2	20	5	12.2±1.5	20	10	49.7±0.2	48.3	50
2nd assessment	14 ± 2	20	5	16 ± 2.5	28.2	10	46.4±1.4	39.6	50

Figure 7.1. Warm thresholds at C5 dermatome.



■,□: Individual patient for the first and second assessment:same patient is connected by either dotted (for improved threshold or continuous line (for unchanged threshold) to demostrate their sensory recovery

Figure 7.2. Cool thresholds at C5 dermatome.



Legends represent same as warm threshold

7.4.2. Referred Sensation

Patients with early referred sensations experienced tingling or "pins and needles" in the arm or hand whilst shaving of the face, touching or tapping the ipsilateral cheek and/or lip. In some cases, thermal or electrical stimuli delivered by TENS could reproduce this response. Two patients (DO and JG) experienced similar sensations in the affected arm or hand when the ipsilateral leg was stimulated.(DO) and further one patient (MB) a referred sensation was experienced in the injured limb when drinking. In most of patients the referred sensations were vague and in only a few (PL &TE) was there complete somatotopic representation of referral in the deafferented limb. Usually most of these were described as vague sensations of "pins and needles", fizzing or dull touching. Some patients reported that referred sensations could be unpleasant with a painful or gripping feeling and some were unaware of any referred sensations until provoked by the investigators. The exact onset of referred sensations seemed difficult for the patients to pinpoint. Some reported early onset but others it did not become manifest until years after the injury (Figure.7.3). For the majority, referred sensations became less strong with time and either remained consistent or disappeared. In others, the intensity did not change, and in a few patients became stronger as the time after injury increased. Referred sensations can be provoked by mechanical stimuli as well as temperature stimuli (Figure. 7.4). Some patients who had undergone intercostal nerve to median nerve, ulnar nerve or nerve to biceps transfer, experienced a referred sensation in the chest when stroking or rubbing the hand or felt a referred sensation in the hand when their chest was stroked, tapped or rubbed. In one patient (TL), coughing produced a squeezing, gripping feeling at the wrist. However, almost half of the patients (48.7%) denied experiencing referred sensation at any time and in these cases referred sensations could not be provoked by the investigators.

Figure 7.3. Onset of referred sensations.

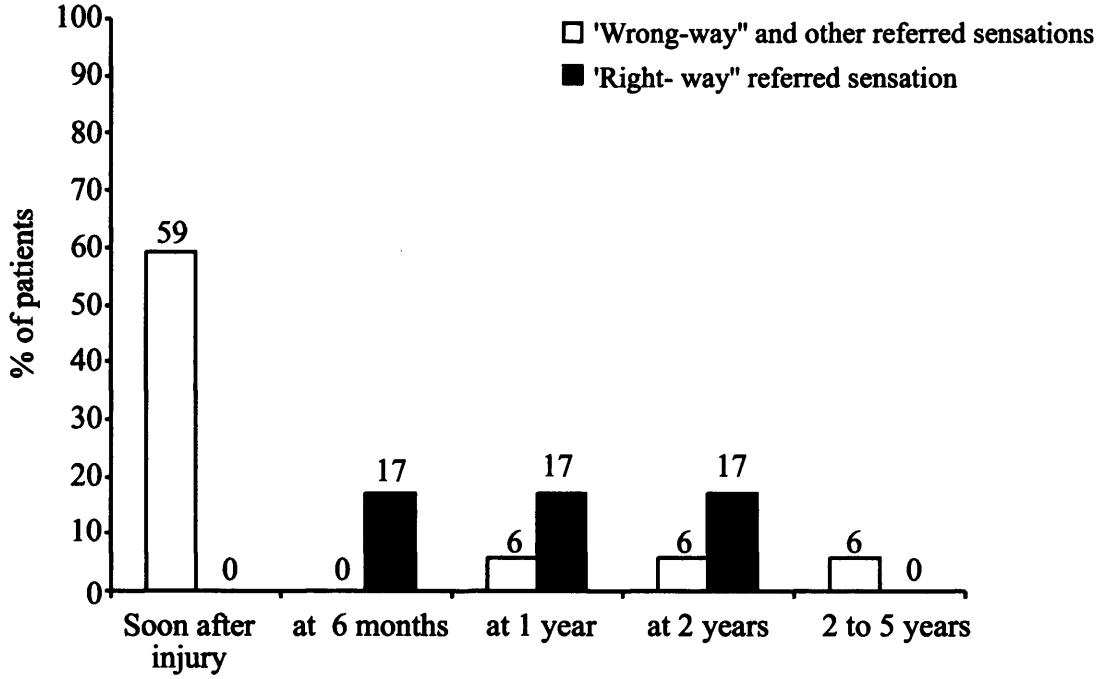
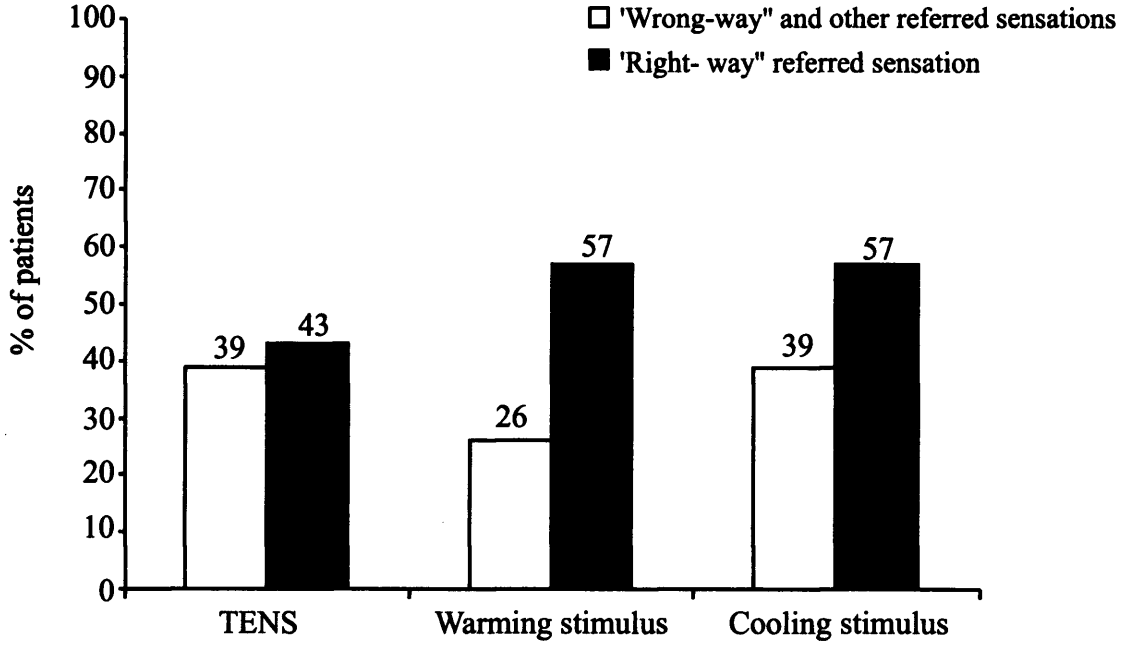


Figure 7.4. Referred sensations produced by other types of stimuli in patients with referred sensations to mechanical stimuli.



7.4.3. Illustrated Cases

Patient MB

MB was a 32 year old male when he sustained injury during motor cycle accident. Nerve roots were avulsed at C5, C6 and C7 and ruptured at C8 and T1 nerve roots. There was Horner's sign on the injured side and clinical evidence of partial Brown-Séquard syndrome although the spinal cord appeared normal. Neither signal changes nor displacement on T1 and T2 weighted MRI examination.

Within 2 weeks of injury, the avulse C5, C6 and C7 nerve roots were re-connected (re-implanted) to the spinal cord and ruptured C8 and T1 nerves were grafted. MB was examined annually for 3 years after injury. He had good motor recovery at the shoulder and elbow, achieving muscle power with average of MRC 3 or MRC 4 in these muscles. Sensory examination showed he had very numb feeling from C6 to T1 and he had lost joint positioning sensation in the injured limb. He was aware of Von Frey hair No. 5 at C5 but could not feel No. 20 from C6 to T1 and No. 3 at T2. Vibration thresholds were >50 V at fingers, wrist and elbow and 32 V at the shoulder. He could not feel <10 °C for cold sensation and > 50 °C for warm sensation from C5 to T1 dermatomes on the injured side. Sweating rates were 11.5 and 23.3 on the right and left palm respectively.

Shortly after his injury he described a distinct referral of sensation when drinking which he felt as though the fluid was flowing down his injured arm and along the ulnar side of his hand although he could still feel the usual swallowing sensation in his oesophagus. Both cold and warm components of the sensation were detected in both regions and did not change with time.

Applied pressure or stroking of the back or chest wall produced a referred sensation in the middle and index fingers. When the patient messaged his pectoral muscles, He sensed a tingling and buzzing sensation in his hand. Stimulation with TENS in similar area failed to reproduce these phenomena. The intensity of these referred sensations decreased over time and thermal stimuli did not provoke referred sensations in subsequent visits.

In his last visit, the area which can provoke the referred sensation shifted to the distal arm and located in a somatotopic pattern. Stroking at the mid lateral part of the arm referred at little finger, stroking at the mid anterior arm region referred to the middle and index fingers and stroking at the more anterior medial surface of arm referred to the middle of the palm, middle and little fingers. TENS did not provoke any referred

sensation. He had phantom sensations soon after injury as if his arm was lying in a different position but without pain.

The patient experienced deafferentation pain describe as continuous, tight, shooting, bursting within 2 weeks of the injury. Pain was experience in the whole upper limb at the beginning but subsequently had pain only at the forearm and hand. Initially pain was severe but has improved. He smoked marijuana, which helped his pain.

Conclusions: The results suggest following deafferentation, there was re organisation in the somatosensory system and that the re-organisation was dynamic since the pattern of referred sensation changed with time. Interestingly, although this patient had referred sensation, taste perception was not involved suggesting that there is no cross- modality plasticity.

Patient PL

PL was a 48 year old male when he sustained injury during a motor cycle accident. His nerve roots were avulsed at C5, C6 and C7, C8 and T1. There was an Horner's sign on the injured side. The spinal cord appeared normal with neither signal changes nor displacement on T1 and T2 weighted MRI examination. .

The accessory nerve was transferred to the musculocutaneous nerve 16 days after injury and intercostal nerves were transferred to serratus anterior and median nerve 6 months after the injury. He was studied twice within 3.5 years after injury. He had good motor recovery at the shoulder and elbow, achieving muscle power of average of MRC 3 or 4 in these muscles. It showed severe numbness feeling from C5 to T1 on sensory examination. He had lost joint position sensation in the injured limb. He could not feel Von Frey hair No. 20 from C5 to T1 but detected No.3 at T2. Vibration thresholds were >50 V at fingers, wrist and elbow and 25 V at the shoulder. Thermal thresholds were increased from C5 to T1 dermatomes on injured side and he was unable to detect <10°C for the cold sensation and > 50°C for the warm sensation. Sweating rates were 12.0 and 41.0 on the right and left palm respectively.

Very soon after injury he experienced referred sensation. Scratching the chest and head of the injured side elicited tingling sensation in the arm which was gradually fading away. After transfer of the intercostal nerve, rubbing the antero lateral part of the chest below the nipple produced tingling in the forearm (the area supplied by median nerve). This sensation was strong initially but faded gradually. The same effect was produced by the application of cold water but not warm water.

Approximately two years after injury, vague sensation was detected at more proximal level (forearm and arm) of injured limb, when his hand was scratched or rubbed. This gradually became more distinct until referred to specific regions e.g. ball of thumb referred to the back of the elbow and mid arm; the index finger (palmer surface) referred to the back of the elbow but slightly anterior to the area referred by the ball of the thumb; the middle finger referred to the ulnar surface of the forearm (middle of the forearm to 4cm above the elbow); the ring finger to the medial aspect of the elbow; the little finger (palmer surface) referred to the ulnar border of the forearm and the ulnar border of the hand referred to the arm and neck. Application of cold or vibration stimuli also referred to similar areas. This patient also felt the motion of water at these areas when his injured hand was placed under running tap water. Stimulation to a similar area with TENS failed to produce the same phenomena. No sensation felt at the hand. There were no phantom sensations.

Within 2 weeks after injury deafferentation pain appeared and was described as continuous, tight, shooting and bursting. Pain was experienced in the whole upper limb at the beginning but subsequently only at the forearm and hand. Initially pain was severe with VAS scores of 10/10 but it has improved and in his last visit VAS scores was 4/10. The improvement of pain coincided with the recovery of muscle function. Gabapentin helped the pain but cannabis and alcohol had no effect.

Conclusions: Once again, the phenomena seen in this patient suggest plasticity. There are different sites: stimulation of head and chest that provoke the referred sensation distally with stimulation of the deafferented hand provoking proximally i.e. forearm and arm. This would imply that there might be plasticity at different levels of the somatosensory system such as within the spinal cord and the brain.

7.5. Discussion

7.5.1. Recovery of sensory function

The clinical characteristics of the sensory dysfunction depend upon the level and etiology of damage and the types of affected nerve fibres. In addition, the peripherally and centrally projecting branch of the sensory axons show a remarkable difference ability of regeneration (Ramer *et al.*, 2001). Sensory innervation patterns are frequently altered following nerve regeneration. For example, touch stimuli are often mislocalised after nerve repair, presumably because the regenerated axons fail to return to their original localisation of the skin. Misdirection of regenerated nerve fibres can sometimes

be corrected by central plasticity but the mechanisms which underline these improvements are poorly understood. The current concept is that the cerebral cortex can reorganise in order to compensate for reinnervation errors in the peripheral nervous system (Wall and Kaas, 1986) .

Sensory recovery was poor in all patients with or without surgical repair especially in nerve root avulsion injury. Only injuries at the C5 dermatome have some recovery mainly of the temperature modalities. However, this recovery may be the result of collateral sprouting from non-injured nerves at the C4 dermatome rather than regeneration induced by repair. Similar recovery was not seen in other dermatomes where adjacent nerves, both above and below, were injured. For example, sensory recovery in C6 and C7 is poor where there is associated damage of C5 and C8. Alternatively, sensory recovery in C5 dermatomes could be simply due to an overlap of the dermatomal distribution (Bear Mark *et al.*, 2001; Polley *et al.*, 1999) rather than to collateral sprouting. The clinical findings presented here are not unexpected and the fact that the recovery of sensibility after nerve repair in adult is nerver perfect, is well documented (Birch, 1998; Lundborg, 2000; Lundborg, 2003). There is a possibility that although a nerve might regenerate reasonably well, there may not be perfect recovery of sensory function. This may not be surprising because it has been shown that there is no correlation between recovery of sensory function and histological evidence of reinnervation (Jabaley *et al.*, 1976). In addition, it is known that sensory receptors disappear after a year of denervation and whilst the regenerating axons reach a target, there may be no receptors to reinnervate (Carlstedt *et al.*, 1986; Dellon, 1976). For reasons mentioned above vibration and thermal sensations are also found to have better recovery at proximal level. Motor recovery at the proximal level is always better than distally and it may well be that recovery of muscle afferent axons contributes to recovery of vibration sensation.

Brachial plexus injuries in neonates show different recovery (Anand and Birch, 2002). Results of repair to obstetric brachial plexus lesions are often disappointing for motor function. This could be related to the relative delay of surgery and a higher rate of motoneurons death than in adults. Sensory recovery is, however, very much better as demonstrated by quantitative sensory testing. While recovery of function after spinal root avulsion in neonates and children was demonstrably related to palliative nerve surgery, they were remarkably different from adults, including excellent restoration of sensory function with evidence of CNS plasticity i.e. perfect localisation of restored sensation in avulsed spinal root dermatomes, presumably reconnected via nerves that

had been transferred from a distant spinal region. Sensory recovery exceeded motor or cholinergic sympathetic recovery.

Patients having dorsal root implantation showed no significant sensory recovery in avulsed nerve roots. Animal studies have shown that it is not possible for axons to re growth into the spinal cord but the dorsal horn neurons can extend new nerve fibres into the implanted dorsal roots (Carlstedt, 1985; Carlstedt *et al.*, 1993; Carlstedt *et al.*, 1987; Carlstedt, 1991b). Such re-growth cannot be entirely ruled out in human being even in those showing poor functional recovery. Nevertheless, the reinnervation of the dorsal root axons seems more successful in neonatal animals and there would be less ability to re growth in adult human (Carlstedt, 1988; Carlstedt, 1991a; Carlstedt, 1997; Carlstedt *et al.*, 1989).

The capacity for regeneration or regrowth within the spinal cord subsequent to surgical repair is important but additional factors play an important role. A lack of growth promoting factors or the presence of inhibitory factors in the central nervous system, have been shown (Chong *et al.*, 1999; Chong *et al.*, 1996; Davies *et al.*, 1997; Davies *et al.*, 1999; McMahon and Kett-White, 1991; Neumann and Woolf, 1999; Ramer *et al.*, 2000; Romero *et al.*, 2001).

7.5.2. Referred sensation

De-afferentation, as a consequence of amputation or brachial plexus injury, can provoke sensory phenomena such as painful or non painful referred sensation (Halligan *et al.*, 1993; Kew *et al.*, 1997; Ramachandran *et al.*, 1992b)

In this study, the underlying mechanisms involved in referred sensation were explored. Re-organization of the somatosensory system after de-afferentation and/or regenerating and sprouting of the sensory axons to vacant synaptic sites within the spinal cord could be responsible for such phenomena.

Although it was traditionally believed that the human central nervous system was hard wired and could not be re-organised, it is now established that this is not the case and the human central nervous system can be re organized after deafferentation (Kaas *et al.*, 1983). The potential for re organization of somatosensory cortex has been shown in animals (Florence *et al.*, 1998) and imaging studies have confirmed that such re-organization is responsible for referred sensations (Kew *et al.*, 1997; Moore *et al.*, 2000). Representation of the trunk and hand, face and chin in the cortex are adjacent to each other (Bear Mark *et al.*, 2001; Jain *et al.*, 1998). There is evidence that following complete or partial lesion of the dorsal columns or peripheral nerves, expansion of

inputs from face and arm into former hand territory occurs (Halligan *et al.*, 1993; Jain *et al.*, 1998; Polley *et al.*, 1999; Ramachandran *et al.*, 1992a). This would provide an underlying mechanism for the face to hand referred sensation seen in patients. However, the distance involved would be too great for regeneration or intraspinal sprouting to occur from the trigeminal nucleus to the dorsal horn of C6 to T1 spinal nerve roots. Although the re-organization of the somatosensory cortex by expansion of an adjacent sensory area of the cortex to the deafferented area could explain such referred sensations, it would not satisfactorily explain referred sensations experienced in the visceral in patients DO and MB, or patients experiencing referred sensation at deafferented areas whilst the ipsilateral normal lower limb were touched (DO and JG). However, it is possible that a large scale re-organization could occur in different levels in the CNS such as the thalamus, brainstem, cuneate nucleus or spinal cord which would explain these types of referral sensation (Banati, 2002; Banati *et al.*, 2001; Grusser *et al.*, 2004; Jain *et al.*, 1998; Jain *et al.*, 2000; Merzenich and Jenkins, 1993; Moore *et al.*, 2000; Pons *et al.*, 1991; Turton and Butler, 2001). It also appears that reorganisation after deafferentation is widespread and probably involved bilateral cerebral structure (Knecht *et al.*, 1995).

In this study, referral of sensation was not experienced by all the patients studied. Some patients were assessed 20 to 40 years after injury and they never had any such sensory experiences. It appears that these who did not have early referred sensation would not experience it in the future. This study has shown that the referred sensation changes in terms of intensity with time. For some patients these referred sensations gradually faded away and others continue to experience them, thus indicating a dynamic nature of plasticity (Garraghty and Kaas, 1992; Knecht *et al.*, 1998). Some of these patients experienced referred sensations soon after injury suggesting the phenomenon may result from unmasking or disinhibiting existing but inactive connections (Borsook *et al.*, 1998). Alternatively, referred sensations experienced later after injury may be due to plasticity as a result of subcortical horizontal sprouting (Kaas *et al.*, 1983).

A further explanation of the phenomenon may be provided simply by regeneration at the different levels of the sensory system. However, in animal studies where sprouting of adjacent intact afferents into denervated areas after extensive dorsal root rhizotomy was examined failed to convincingly demonstrate neuronal growth into the deafferented region even though abundant "vacant" synaptic sites are created (McMahon and Kett-White, 1991; Rodin and Kruger, 1984; Rodin *et al.*, 1983). Inducing afferents into a growth or regeneration mode by a peripheral conditioning nerve injury at the time of initial lesion produces an expanded central terminal field representation (McMahon and Kett-White,

1991) (Molander C, 1988) and these are able to elicit responses in postsynaptic neurons (Molander C, 1997). Such sprouting could explain certain types of referred sensation for example the sensation produced in the hand when stroking the intact intercostal dermatome (T2) after intercostal nerve transfer (T3, T4 and T5) to the ulnar nerve some years after the operation. However it is difficult for patients with this referred sensation to notice accurately such a pattern of evolving sensory sensation in the T6 to T2 dermatome area. This can be further complicated by the fact that the dermatomes distribution overlaps (Bear Mark *et al.*, 2001). This makes it is difficult to detect an evolving, ascending sensation from T6 to T2 and to prove that this particular referred sensation is a result of the regeneration by sprouting rather than plasticity.

Furthermore, patients who had this particular referred sensation showed no evidence of sensory recovery in their hands (i.e. evidence of regeneration at the injured peripheral nerve, although the possibility of intraspinal sprouting cannot be excluded).

In general referred sensation might also occur in the uninjured individual as a peculiar sensory phenomenon referred to as "Mitempfindung"(Bean, 1981; Evans, 1976; Richter, 1977; Schott, 1988; Sterling, 1973). However, this phenomenon usually occurs in healthy individuals and the characteristic symptoms are quite different though the mechanism was postulated as centrally mediated.

In some cases, referred sensation appears to indicate an early sign of recovery of nerve transfer particularly in intercostals nerve transfer (Chuang *et al.*, 1992). Sensory stimulation of the limb provoking the sensation at the chest indicates that following repair nerves are crossed so that stimuli delivered to the recipient sites are referred to donor sites. These findings are consistent with other studies and also indicate that changes in peripheral innervation are not easily corrected by cortical circuits leading to the primary cortex (Wall and Kaas, 1986). By contrast, it seems that in one patient (PL), the somatosensory system remains able to process and remember accurately, information from years after the deafferentation (Jain *et al.*, 1998; Schady *et al.*, 1994). This also indirectly supports the view that supraspinal neurons remain capable of carrying the message after injury of peripheral nerve (Wang *et al.*, 2000).

Neurophysiological proof that somatotopic changes occur or that they would reflect functional consequences manifest as referred sensation, remain to be shown (Dostrovsky, 1999; Moore and Schady, 2000).

Interestingly, there is no relationship between chronic neuropathic pain and referred sensation although the underlying mechanism for both phenomena is thought to be plasticity in the nervous system as discussed above. Whilst there is strong correlation between the degree of cortical reorganisation and the magnitude of phantom limb pain, no such correlation was found in non- painful, phantom phenomena. Different neural substrates might be responsible for painful and non- painful phenomenon (Flor *et al.*, 1995; Flor *et al.*, 2000; Grusser *et al.*, 2001; Knecht *et al.*, 1995) with genetic factors playing a role (Melzack, 1999).

Technical limitations of the study

In this study a single investigator carried out the QST for all patients in order to ensure reproducibility.

Although QST is a very useful tool for repeated sensory testing, it has limitations. QST tests the integrity of the entire sensory neuraxis, but has no localising value. As a psychophysical test, it therefore, lacks the objectivity of conventional nerve conduction study (NCS) (Chong and Cros, 2004). Abnormality detected in the QST must be interpreted in the context of a thorough clinical examination and other appropriate tests such as electromyography(EMG) and NCS (Shy *et al.*, 2003).

In addition to a thorough clinical neurological examination for the evaluation of sensation, application of quantitative sensory testing (QST) can help to establish accurate "thresholds for sensory perception". This approach enables the presence and degree of a sensory deficit to be measured (Stewart and Freeman, 2002). Unlike conventional nerve conduction studies, QST can assess for function of all size of peripheral nerve fibres (Table 7.2) (Stewart and Freeman, 2002; Yarnitsky, 1997; Zaslansky and Yarnitsky, 1998). In addition, QST has advantage that it can access sensory receptors, the distal nerve fibre, and the entire peripheral and central sensory nerve circuit. Using QST, sensory deficit can be quantified and the data used for statistical analysis. However, QST is a psychophysical test, relying on the co-operation, alertness and ability of the patient to follow instruction (Chong and Cros, 2004).

In this study, sensory thresholds were determined using the method of limits with dynamic stimuli, including reaction time, for the response. This method may over estimate sensory thresholds and the results tend to be variable because of the need for full co-operation of patient with constant vigilance (Chong and Cros, 2004).

Table 7.2. Sensory Stimuli and Nerve Fibre Types Commonly Assessed in QST and Sensory Nerve Conduction Studies.

Sensory Stimuli	Nerve Fibre Type
Vibration	Large myelinated
Cold	Small myelinated
Warm	Non myelinated
Heat pain	Small myelinated and non myelinated
Cold pain	Small myelinated
Electrical Current	
High frequency (250 to 2000Hz)	Large myelinated
Low frequency (5 Hz)	Non myelinated
Sensory Nerve Conduction Studies	Large myelinated

Conclusions

Recovery of different somatic sensory modalities after traction brachial plexus injury is not promising despite dorsal root re-implantation. Recovery of sensory function depends not only on technically successful nerve repair but also upon the important role of plasticity in the CNS. In order to promote regeneration and functional reconnection and achieve any degree of functional recovery of sensation, there are measures which need to be considered. These include manipulation of the biological environment and seeking strategies to facilitate re-organisation in the CNS.

Chapter VIII: Pain phenomena following brachial plexus avulsion injury and surgical repair

8.1. Summary

Pain relief in patients (n=76), with severe brachial plexus avulsion injury repaired by different surgical techniques was studied, using questionnaires and quantitative sensory testing. This study confirmed that (1) the severity of pain is related to the number of avulsed nerve roots, and (2) successful surgical repair, including a new method which re-connected avulsed spinal nerve roots directly to the spinal cord, improved pain. Allodynia was observed mainly in border-zone of affected and unaffected dermatomes, in 18 % of patients studied at early (< 6 months) and 37 % patients at a later stage (9 months to 41 years), to the following stimuli: warm (11% early, 20.0% late), cool(4% early, 9% late), dynamic mechanical (8% early, 21% late) and static mechanical (12 % early, 16% late). This study concluded that a novel method of surgical repair, re-implantation could improve pain in patients with severe injuries to the brachial plexus. It appears that following deafferentation, the relationship between plastic change, occurring in the nervous system, and chronic neuropathic pain is far more complex than previously thought and an understanding of the mechanisms involved will help to develop treatment programs which will improve the management of chronic neuropathic pain.

8.2. Introduction

There have been few studies of pain which occurs as a consequence of injury to the brachial plexus. These have been shown that pain following brachial plexus injury is intractable and difficult to treat, but ameliorated by successful surgical repair (Berman *et al.*, 1996; Berman *et al.*, 1998). In those studies, patients who had undergone the usual repair of spinal cord root avulsion injuries, by transfer of an intact neighbouring nerve to the distal stump of the damaged nerve were observed. A novel surgical strategy for re-implanting avulsed spinal roots or nerve grafts to the spinal cord has recently been applied in patients with severe brachial plexus injury, (Carlstedt *et al.*, 2000). The result of this innovative surgical repair is included in this present study. There are distinct aspects of plexus injuries which may involve both the central and distal axons of sensory neurones at different spinal root levels. Chronic pain occurs in about 5 % of patients with peripheral nerve injury (Sunderland, 1978)(Sunderland,

1993). This also applies to patients with plexus injuries where the lesion is distal to the dorsal root ganglion.

Peripheral as well as central mechanisms contribute to the generation of neuropathic pain (Attal and Bouhassira, 1999; Campbell, 2001; Coderre *et al.*, 1993; Jensen *et al.*, 2001; Melzack *et al.*, 2001; Woolf, 2004). In some patients, sensory stimulation (thermal and mechanical) within the avulsed dermatome is perceived abnormally, or experienced at remote sites with or without phantom sensations. This is also thought to be related to the re-organisation of the somatosensory system which occurs following deafferentation (Condes-Lara *et al.*, 2000; Flor *et al.*, 1995; Flor *et al.*, 2000; Kaas, 2000; Malin and Winkelmuller, 1985; Moore *et al.*, 2000; Ramachandran and Hirstein, 1998).

However, there have been only few studies which investigate the relationship between pain, referred sensation and cortical re-organisation after deafferentation (Flor *et al.*, 1995; Grusser *et al.*, 2001; Knecht *et al.*, 1995). Furthermore, to our knowledge, there is no study, which examines whether the severity of "deafferentation" pain can be related in any way with referred sensation.

In this study, the relationship between pain and surgical repair was assessed. The novel method of surgical repair, re-implantation for improving pain in severe brachial plexus injury was also examined. The relationship between referred sensation and the severity of deafferentation pain following spinal nerve root injury was also investigated.

8.3. Methods

8.3.1. Patients

Patients (n=76) who had sustained brachial plexus injury were studied after written consent and local ethics committee approval. The patients were referred to the Peripheral Nerve Injury Unit, Royal National Orthopaedic Hospital, London, UK and clinical assessments and neurophysiological studies were performed at the Hammersmith Hospital, London, UK. Informed consent was taken from all patients.

Exclusion criteria, investigations for the diagnosis and the study of subjects are detailed in Chapter VII.

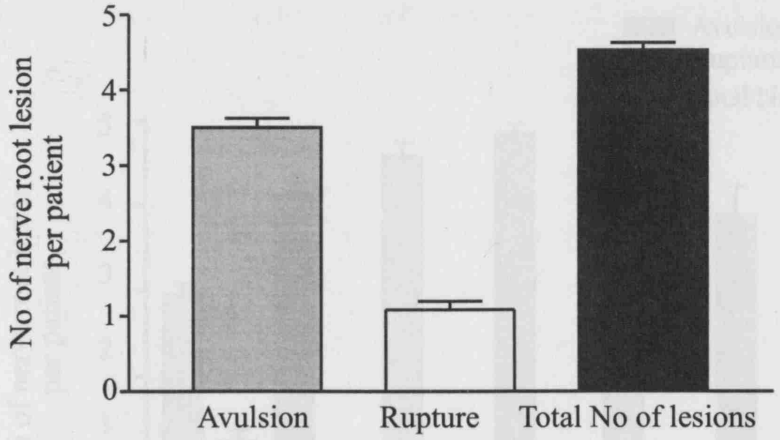
The patients (of which seventy two were male) who had sustained brachial plexus injury were assessed at different times after injury. The detailed pattern of the lesion for each study subjects in this study is shown in Table 8.1 and the means number of spinal nerve root lesions is shown in Figure. 8.1.

Table 8.1. Lesions of the brachial plexus.

Lesion					No of patients
C5	C6	C7	C8	T1	
A	A	A	A	A	12
R	A	A	A	A	10
R	R	A	A	A	9
R	R	R	A	A	3
R?	A	A	A	A	2
Intact	Intact	A	A	A	2
R	R	A	A	?A	2
R	A	A	Intact	Intact	2
A	A	Intact	Intact	Intact	2
A?	A	A	A	A	1
R	A?	A	A	A	1
Pre ggl R	Pre ggl R	A	A	A	1
R?	R?	A	A	A	1
R	?A	?A	A	A	1
Pre ggl R	Pre ggl R	LIC	A	A	1
A	A	A	R	A	1
R	A	R	R	A	1
A?	A?	A?	A?	?A	1
A	A	A	A?	?A	1
R	LIC	A	A	?A	1
A	A	A	R	R	1
A	A	R	R	R	1
R	A	A	A	R	1
A	A	A	LIC	LIC	1
R	A	A	LIC	LIC	1
Partial A	A	A	A	LIC	1
A	A	LIC/R	LIC	LIC	1
A?	A?	A	LIC	LIC	1
A	A	A	A	LIC	1
A	A	Intradural R	Intact	Intact	1
A	A	A	Intact	Intact	1
R	Pre ggl R	A	A?	Intact	1
R?	A	A	A?	Intact	1
R	A	A	A	Intact	1
R	R	A	A	Intact	1
A	A	A	*	*	1
R	R	A	A	?	1
?R	A	A	A	?Intact	1
R	R	A	A	Intradural R	1
R	R	A	A	?	1
R	A	A	Recovering	Recovering	1
Total number of the patients					**76**

A; avulsion, R; rupture, ggl; ganglionic, *dorsal root damage? Pre ggl R; Preganglionic rupture

Figure 8.1. Mean number of spinal nerve root lesions.



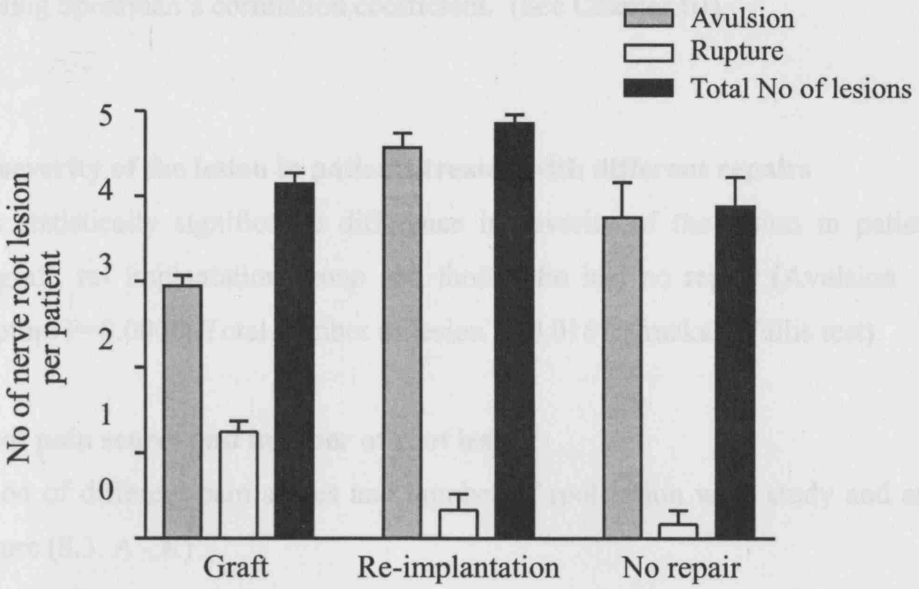
Mean ± SEM total of spinal nerve lesion is 4.5 ± 0.1 and the mean ± SEM number of avulsion is 3.5 ± 0.1 (Range: minimal 2 spinal nerve roots avulsion and maximum 5 spinal roots avulsion).

Most patients had more than one type of repair operation and mean ± SEM severity of the lesion per is shown in Table 8.2 and Figure 8.2.

Table 8.2. Mean severity of the lesion in patients treated with different repairs.

Method of repair	Type of lesion		
	Avulsion	Rupture	Total No. of lesions
Graft and other nerve transfer (n = 54 patients)	3.0 ± 0.1	1.3 ± 0. 1	4.1 ± 0.1
Re-implant and nerve transfer (n = 14patients)	4.6 ± 0.2	0.3 ± 0. 2	4.9 ± 0.1
No surgical repair (n = 8 patients)	3.8 ± 0.4	0.2 ± 0. 2	3.9 ± 0.4
P values (Kruskal-Wallis test)	0.0001	0.0005	0.02

Figure 8.2. Mean severity of the spinal nerve roots injury in patients treated with different repairs.



8.3.2. Sensory testing

The details of sensory tests, including quantitative sensory testing are discussed in the previous Chapter III. The method of observation of "referred sensations" is also discussed in Chapter III.

8.3.3. Pain History

The "avulsion" or de-afferentation pain is characteristically constant and crushing, usually felt in the hand with intermittent bursts of pain shooting down the arm. It may occur within days from the time of injury, and is often intractable, lasting from months to years, or even decades.

Pain was assessed by interviewing the patients directly using the McGill Pain Questionnaire and visual analogue pain scores. (current pain intensity, minimum and maximum (Melzack, 1975).

Statistics: The Mann-Whitney U and the Kruskal-Wallis tests were used. *P*-values <0.05 were considered to be significant. Data are presented as mean ± SEM (standard error of mean) unless otherwise stated. Pain scores were correlated with other parameters using Spearman's correlation coefficient. (See Chapter III)

8.4. Results

8.4.1. Mean severity of the lesion in patients treated with different repairs

There was a statistically significance difference in severity of the lesion in patient repaired by graft, re- implantation group and those who had no repair (Avulsion P <0.0001; Rupture P=0.0005; Total number of lesion P=0.0167;Kruskal-Wallis test).

Correlation of pain scores and number of root lesion

The correlation of different pain scores and number of root lesion were study and are shown in Figure (8.3. A - K)

There was a significant correlation between the intensity of pain (current VAS score) and the number of avulsions ($p = 0.0004$; $r = 0.3564$) and intensity of pain and the total number of lesions ($p = 0.03$; $r = 0.22$). No correlation was found between VAS (MIN) and the number of avulsions ($p = 0.9$; $r = 0.01$) or the total number of lesions ($p = 0.7$; $r = 0.04$). There was also no correlation found between VAS (MAX) and the number of avulsions ($p = 0.6$; $r = 0.05$) or the total number of lesions ($p = 0.4$; $r = - 0.09$). However, there was a correlation between severity of injury, in terms of the number of spinal nerve root avulsions ($p = 0.01$; $r = 0.26$) and the sensory component of the McGill sensory score, but not with the total number of lesions ($p = 0.1$; $r = 0.15$). There was also a correlation between severity of the injury in terms of the number of spinal nerve root avulsion ($p = 0.02$; $r = 0.24$) and the McGill total score but not with the total number of lesions ($p = 0.2$; $r = 0.15$).

Figure 8.3. Correlation of pain score and severity of injury.

Figure 8.3A. Correlation of pain score (VAS -current) and severity of injury (number of root avulsion).

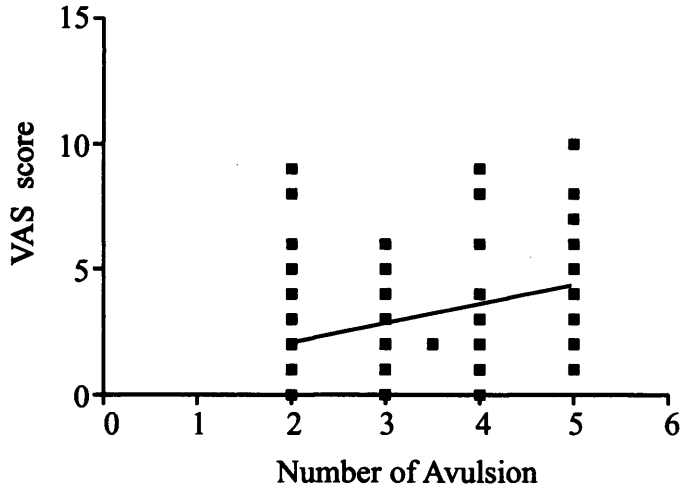


Figure 8.3B. Correlation of pain scores (VAS -minimum) and severity of injury (number of root avulsion).

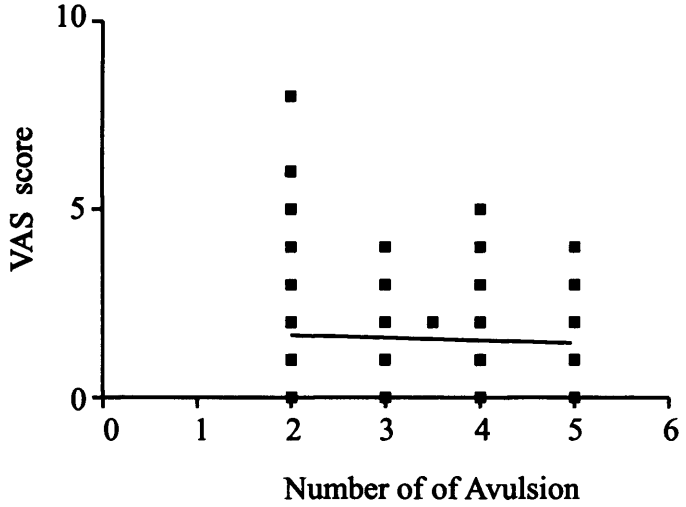


Figure 8.3C. Correlation of pain scores (VAS –maximum) and severity of injury (number of root avulsion).

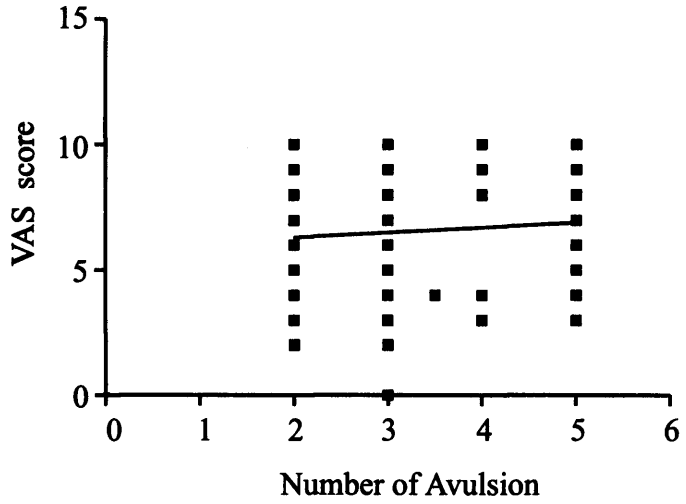


Figure 8.3.D. The correlation of pain scores (McGill-sensory) and severity of injury (number of root avulsion).

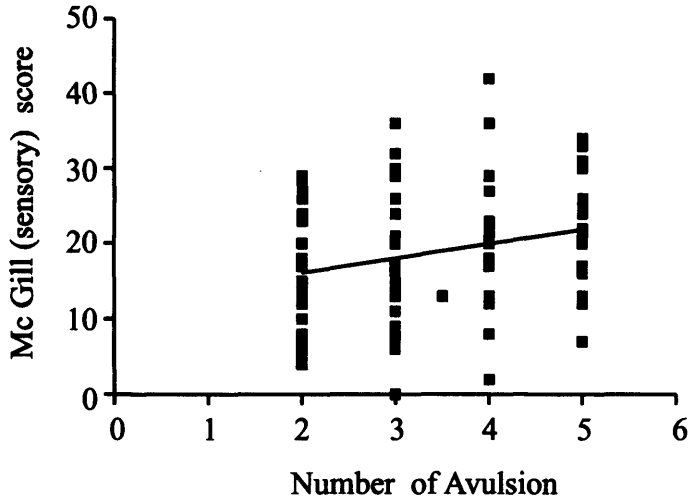


Figure 8.3E. The correlation of pain scores (McGill-total) and severity of injury (number of root avulsion).

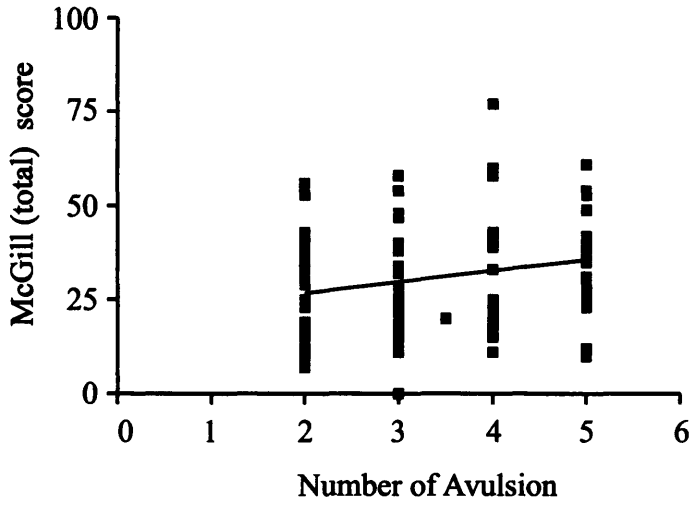


Figure 8.3F. The correlation of pain scores (VAS-current) and severity of injury (total number of root lesion).

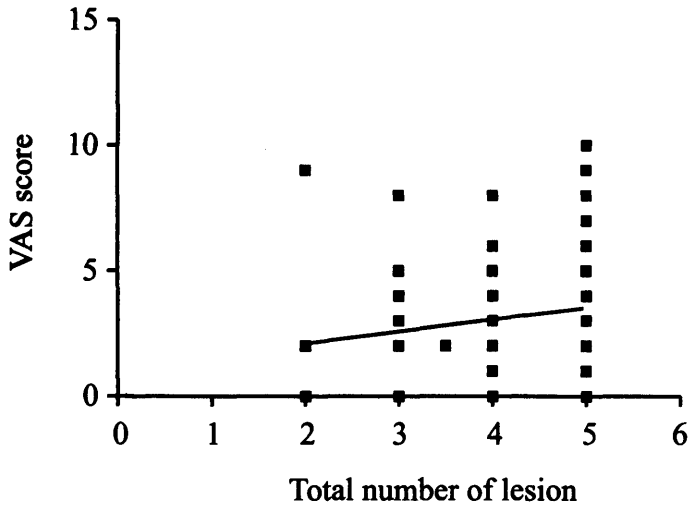


Figure 8.3G. The correlation of pain scores (VAS- minimum) and severity of injury (total number of root lesion).

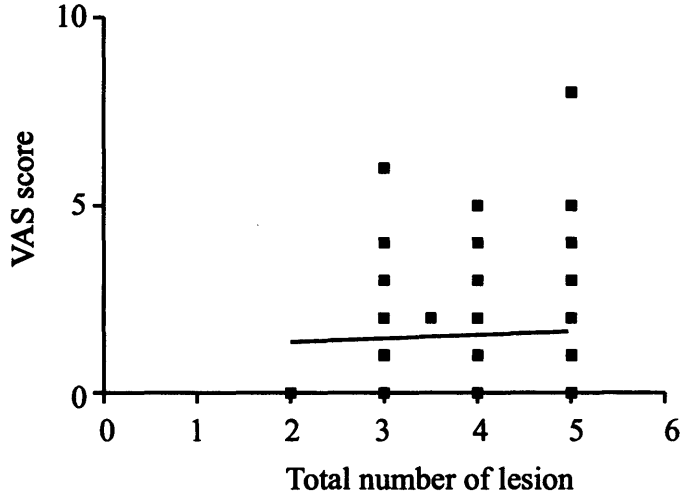


Figure 8.3H. The correlation of pain scores (VAS- maximum) and severity of injury (total number of root lesion).

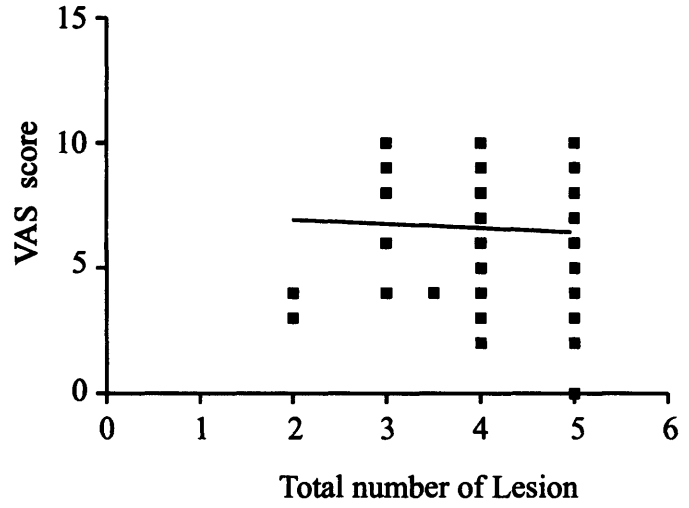


Figure 8.3I. The correlation of pain scores (McGill-sensory) and severity of injury (total number of root lesion).

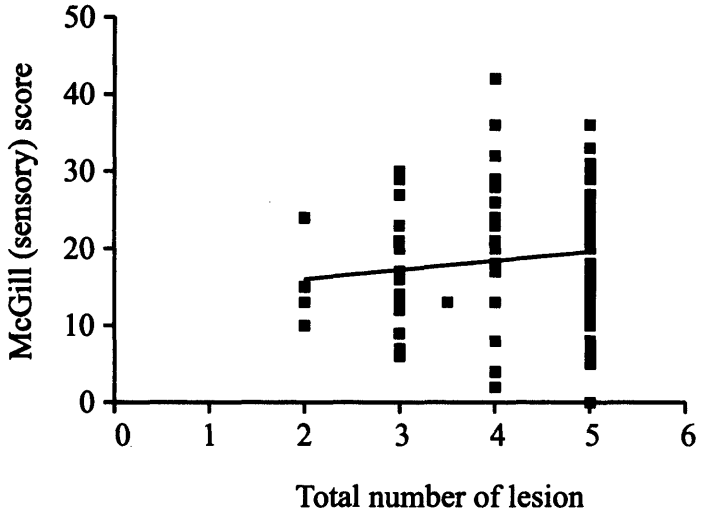
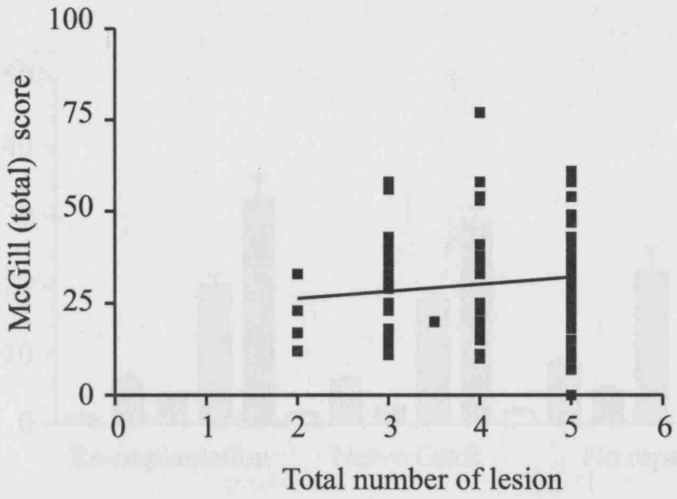


Figure 8.3J. The correlation of pain scores (McGill-total) and severity of injury (total number of root lesion).



Severity of Pain after different surgical repairs

Pain was least severe in the patient group repaired by graft and nerve transfer and greatest in patients without surgical repairs (Table 8.3).

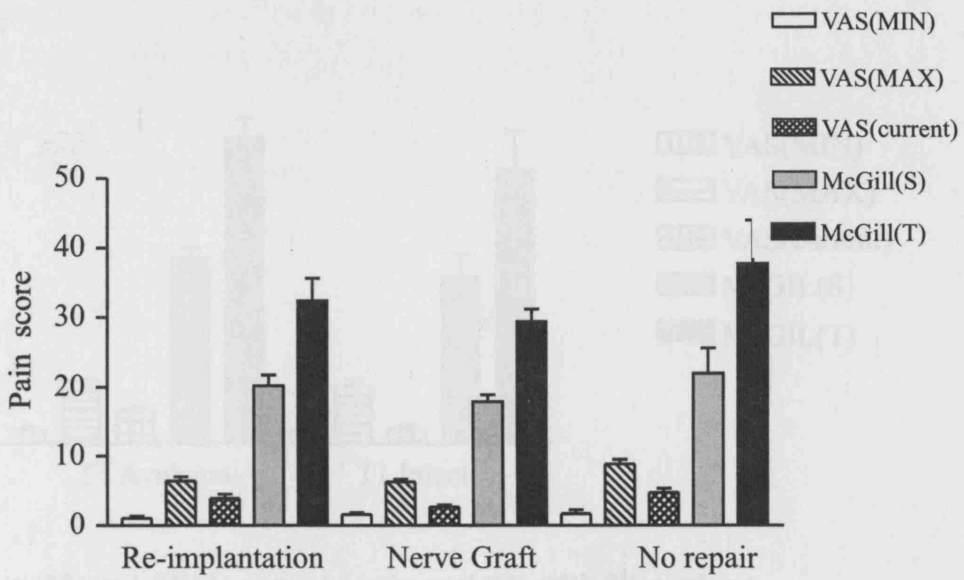
In patients repaired by graft and transfer or re- implantation and transfer the VAS (MAX and Current) pain scores were significantly different from those without repair (VAS - MAX, P = 0.02; VAS - Current P=0.01) but pain scores measured as VAS (MIN), Mc Gill (S) or McGill (T) were unchanged (VAS - MIN, P = 0.3; McGill - S, P=0.5; McGill - T, P = 0.4; Kruskal-Wallis test).

Table 8.3. Pain scores (mean ± SEM) for patients repaired by different methods.

	VAS (Current)	VAS (MIN)	VAS (MAX)	McGill (S)	McGill (T)
Graft and transfer	2.7 ± 0.3	1.7 ± 0.2	6.3 ± 0.4	17.9 ±1.0	29.4 ± 1.8
Re-implantation and transfer	4.0 ± 0.6	1.1 ± 0.4	6.5 ± 0.6	20.2 ±1.6	32.4 ± 3.2
No surgical repair	4. 8 ± 0.6	1. 8 ± 0.5	8. 9 ± 0.7	22.0 ± 3.6	37.8 ± 6.2
P values (Kruskal-Wallis test)	0.01	0.3	0.02	0.5	0.4

VAS, visual analogue scale; MIN, minimum; MAX, maximum; S, sensory; T, total

Figure 8.4. Pain scores for patients repaired by different methods.



Pain scores in patients with avulsed or intact T1

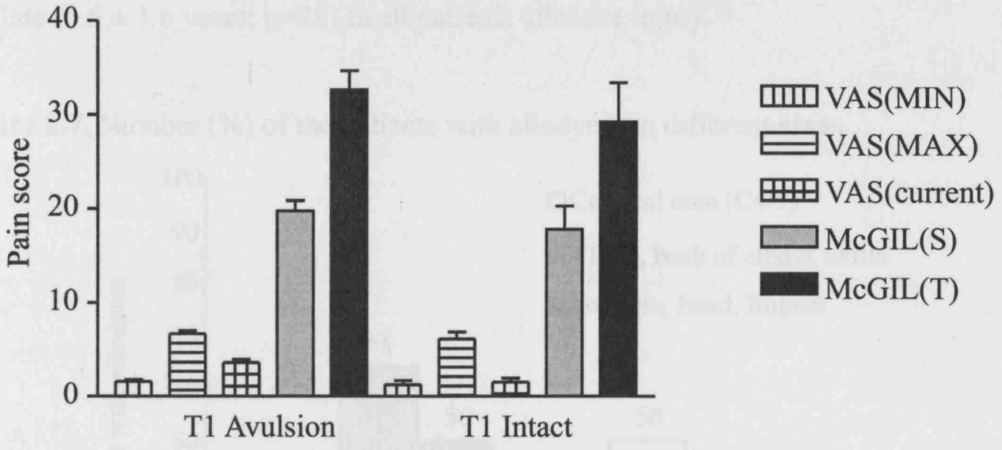
Pain scores for patients with avulsed or intact T1 are shown in (Table 8.4). Pain, as recorded on VAS (current), is worse in patients with T1 spinal nerve root avulsion compared to those with intact T1.There was no statistically significant difference of VAS (MIN), VAS (MAX), McGill (S) and McGill (T) score in patients with avulsed or intact T1 but of VAS (current) was statistically different in these groups. (Mann Whitney U test)

Table 8.4. Pain score(mean ± SEM) in patients with avulsed or intact T1.

	VAS (Current)	VAS (MIN)	VAS (MAX)	McGill (sensory)	McGill (total)
T1 root avulsion (n= 51patients)	3.6 ± 0.3	1.6 ± 0.2	6.6 ± 0.4	19.8 ± 1.1	32.6 ± 2.0
Intact T1 (n= 15 patients)	1.5 ± 0.4	1.3 ± 0.4	6.1 ±0.8	17.8 ± 2.5	29.2 ± 4.2
P values (Kruskal-Wallis test)	0.003	0.3	0.6	0.4	0.3

T1, First thoracic spinal nerve root; VAS, visual analogue scale; MIN, minimum; MAX, maximum; S, sensory; T, total

Figure 8.5. Pain score in patients with avulsed or intact T1.



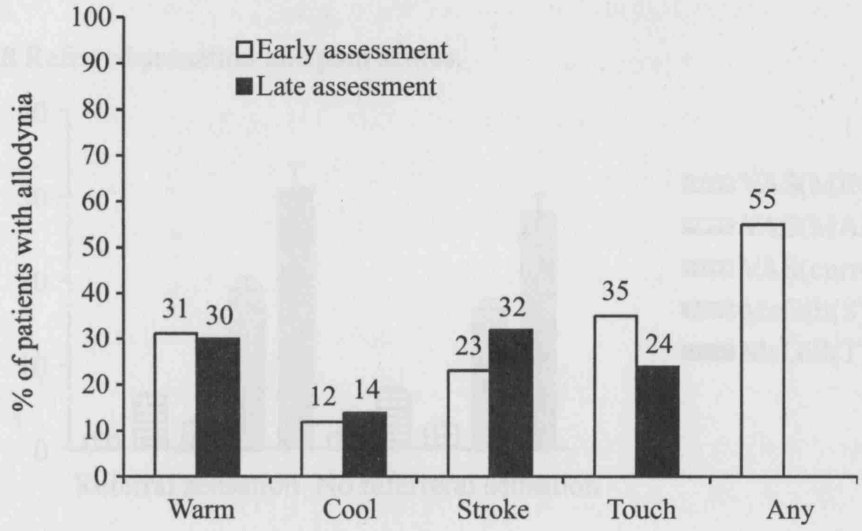
Total number (Mean ± SEM) of avulsion in patients with T1 avulsion

The total number of avulsion in patients with T1 avulsion is 3.8± 0.1 and patients with intact T1 is 2.2 ± 0.1. There is **statistically significant** difference in total number of avulsion in patients with T1 avulsion and intact T1. (P<0.0001) (Mann-Whitney U test)

8.4.2. Allodynia

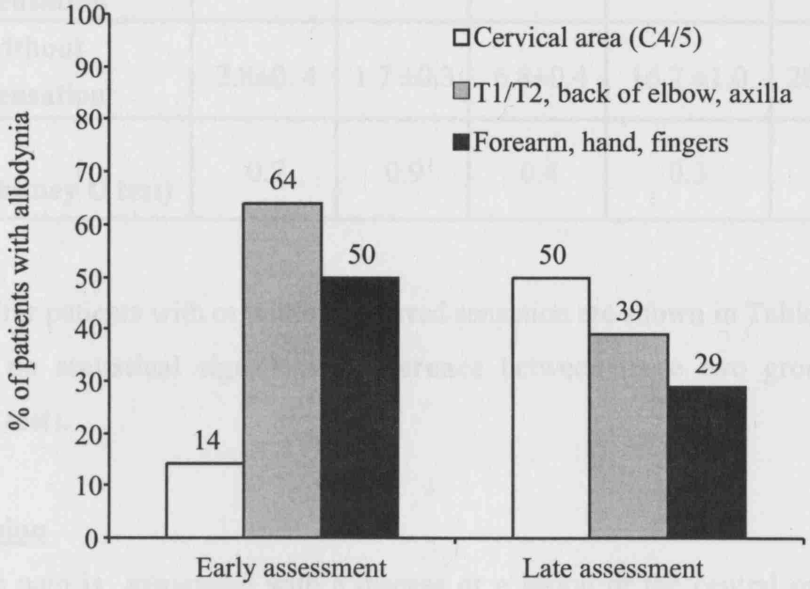
Following injury, 42 of 72 patients experienced allodynia provoked either by mechanical or thermal stimuli. Patient could suffer either from allodynia provoked by a specific stimulus or from a combination of various stimuli. The number of patients with each type of allodynia and the affecting regions of allodynia are shown in Fig. 8.6 and Fig. 8.7.

Figure 8.6. Number (%) of patients showing different types of allodynia.



Percentage of patients showing different types of border zone allodynia; modality specific and any modality. Assessments were carried out early (4.0 ± 0.6 months; n=14) and late (6.5 ± 1.6 years; n=28) in all patients after the injury.

Figure 8.7. Number (%) of the patients with allodynia in different areas.



Percentage of different areas (border zones) of allodynia for any modality. Assessments were carried out early (4.0 ± 0.6 months; n=14) and late (6.5 ± 1.6 years; n=28) in all patients after the injury. (Note; each patient can have allodynia in more than one area).

8.4.3. Referred sensation and pain

The severity of pain in patients with or without referred sensation is shown in Figure. 8.8 and Table 8.5.

Figure 8.8 Referred sensation and pain scores.

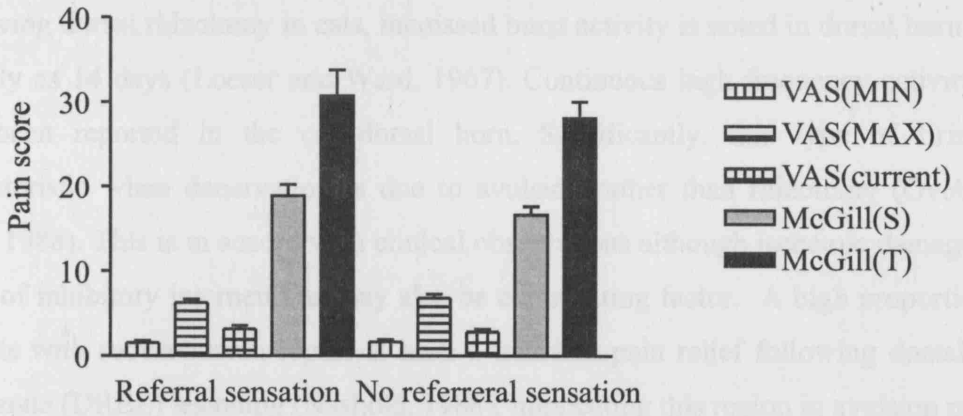


Table 8.5. Pain score (mean ± SEM) in patients with or without referred sensation.

Patient type	VAS (current)	VAS (MIN)	VAS (MAX)	McGill (sensory)	McGill (total)
Patients with referred sensation	3.2 ± 0.4	1.6± 0.2	6.3 ± 0.4	18.9 ± 1.3	30.7 ± 3.1
Patients without referred sensation	2.8±0. 4	1.7 ±0.3	6.8±0.4	16.7 ±1.0	28.1± 2.0
P values (Mann Whitney U test)	0.7	0.9	0.4	0.3	0.6

Pain scores for patients with or without referred sensation are shown in Table 8.5. There was **no statistical significant difference** between these two groups **(Mann Whitney U test).**

8.5. Discussion

Neuropathic pain is associated with a disease or a lesion of the central or peripheral nervous system (Jensen *et al.*, 2001). Neuropathic pain in association with traction lesions of the brachial plexus is perhaps the most severe, most persistent and most resistant to treatment (Birch *et al.*, 1998). There are several independent, peripheral and central mechanisms responsible for generation of neuropathic pain (Baron, 2000b; Dotson, 1997; Woolf, 2004). Distinct mechanisms are involved in pain following spinal cord root avulsion. In traction lesions of the adult brachial plexus, rupture is usually peripheral to the PNS-CNS transition region of the root. However, some avulsion injuries cause damage central to the transitional region which may results in "central pain". There is evidence that pain experienced after brachial plexus avulsion injury parallels the generation of abnormal activity within the dorsal horn of the spinal cord. Following dorsal rhizotomy in cats, increased burst activity is noted in dorsal horn cells as early as 14 days (Loeser and Ward, 1967). Continuous high frequency activity has also been reported in the cat dorsal horn. Significantly, this type of firing is characteristic when denervation is due to avulsion rather than rhizotomy (Ovelmen-levitt, 1988). This is in accord with clinical observations although ischemic damage and death of inhibitory interneurons may also be contributing factor. A high proportion of patients with root avulsion report at least a transient pain relief following dorsal root entry zone (DREZ) lesioning (Nashold, 1988), implicating this region in avulsion pain.

There is clinical and experimental evidence which indicates that central neuroplasticity plays a significant role in the development of pathological pain such as spontaneous pain and allodynia (Coderre *et al.*, 1993). Severe pain is usual in patients after preganglionic injury, and for some, it is an overwhelming problem that dominates their life (Birch, 2003). The majority of patients with spinal cord root avulsion injury (i.e. central axotomy) report severe chronic pain at some point in the course of their condition and this "avulsion" or de-afferentation pain is characteristically constant and crushing, usually felt in the hand in patients with brachial plexus injury, with intermittent bursts of pain shooting down the arm (Birch *et al.*, 1998; Wynn Parry, 1980). It may occur from the time of injury or more generally within days, and is often intractable, lasting from months to years, or even decades. The severity of pain is related to the extent of the lesion (Berman *et al.*, 1998; Birch *et al.*, 1998) and there is a relation between pain and recovery of function following operative repairs (Berman *et al.*, 1998).

In this study, there was a significant correlation between intensity of pain (current VAS score) and severity of the lesion, but no correlation between VAS (Minimum and Maximum) and the severity of lesion. An explanation for this might be that the current pain reflects a constant background pain and patients would be using the VAS (Minimum and Maximum) scores for the paroxysmal, periodic pain. There was also a significant correlation between severity of injury in terms of the number of spinal nerve root avulsions, and the sensory component of the McGill score as in a previous study (Berman *et al.*, 1998). There was a positive, but not statistically significant correlation between severity of injury in terms of the total number of spinal nerve root lesions, and the sensory component of the McGill score. The correlation is not as clear with total Mc Gill scores, since several subjects have significant, affective, emotional and miscellaneous components which again is consistent with previous findings (Berman *et al.*, 1998). It was also reported that patients with neuropathic pain have higher sensory, discriminative scores compared to all other groups such as those suffering from cancer, headache etc (Majani G, 2003).

This study confirms previous findings of a correlation between severity of pain and extent of nerve injury (Berman *et al.*, 1998; Wynn Parry, 1980). The group of patients repaired with re-implantation and other nerve transfer had the most severe lesion and the group of patients who was repaired with graft and transfer had the least severe lesion. It is therefore not surprising that patients who were repaired with graft and

transfer had the least severe pain. However, patients having re-implantation and other nerve transfer suffered less severe pain than those without any surgical repair although the former group had more severe lesion than the latter. There is evidence that pain can be improved after surgical repair regardless of recovery of muscle function although the mechanism of this pain relief is not clear (Berman *et al.*, 1996; Berman *et al.*, 1998). In a previous study, pain was improved in some patients repaired by re-implantation (Carlstedt *et al.*, 2000; Carlstedt *et al.*, 2004). In the present study, there was an opportunity for the first time, to compare the improvement of pain in patients after re-implantation and other nerve transfer with a non-operated control group. This present study now demonstrated that a novel method of surgical repair-re-implantation could improve pain following severe brachial plexus injury. There are several clinical and experimental studies showing that motor neurone regeneration occurred after re-implantation of avulsed spinal nerve roots (Carlstedt *et al.*, 2000). How regeneration of motor neurones improve deafferentation pain in ventral root implantation without repair of dorsal root repair is difficult to explain. There are sensory receptors in deeper somatic structures (proprioceptors) (Ropper Allan *et al.*, 2001), and it is reasonable to assume that recovery of proprioceptors in re-innervated muscles would alleviate deafferentation pain. From the present study it can be concluded that nerve repair reduces pain after spinal root avulsions, and that the mechanism involves restoration of peripheral inputs (e.g. from muscle), or central connections after successful regeneration. Although afferent and efferent fibres are traditionally thought to join the spinal cord separately in ventral and dorsal spinal nerve roots, this study provides further clinical evidence that the ventral root can carry afferent fibres, which has been shown by previous studies (Birch *et al.*, 1998; Schenker and Birch, 2000). Those afferent fibres have not been demonstrated to enter the spinal cord through the ventral root. Contrary to the findings in adult, there was remarkably, no evidence of long-term chronic pain behaviour or neuropathic syndromes in children, although pain to external stimuli was reported normally in unaffected regions (Anand and Birch, 2002). In neonates, it may well be that differences are related to later maturation of injured fibres, and that CNS plasticity (e.g. sprouting or maturation of descending inhibitory tracts) may account for their lack of long-term chronic pain after spinal root avulsion injury.

Patients with T1 lesion have decreased sympathetic activity such as axon-reflexes and reduced sweating rates on the injured side. In the present study, there was a relationship between pain and T1 spinal nerve root avulsion unlike previously reported (Berman *et al.*, 1998). The most severe pain was seen in patients with T1 spinal nerve root avulsion

compared to those with intact T1 nerve root which is contrary to the findings that concepts that sympathectomy can be effective for the treatment of neuropathic pain (Birch *et al.*, 1998). However, patients with T1 avulsion had a more severe lesion than those with intact T1 and this may provide an explanation for this finding.

In approximately a third of patients with avulsion injuries there was allodynia to mechanical and thermal stimuli between the injured and intact dermatomes (border-zone), prior to any surgical nerve repair. Usually this is clinically mild and often not noticed by the patient, and may require quantitative sensory testing to be revealed. A few patients may demonstrate more severe allodynia and hyperalgesia after spontaneous or post-surgical sensory recovery, with features similar to partial nerve injury. Abnormally sensitised, peripheral nociceptive fibres can induce secondary changes in the anatomic reorganization of the dorsal horn and central processing leading to spinal cord hyper- excitability and produced allodynia (Baron, 2000a; Baron, 2000b). Intact nociceptors of adjacent, uninjured, spinal nerves acquire abnormal, spontaneous activity and a chemical sensitivity may play a role in creating or maintaining this abnormal pain state (Campbell, 2001).However, ongoing nociceptive system is not essential to maintain central plasticity in order to produce mechanical allodynia (Baron and Maier, 1995; Baron and Saguer, 1995).

Interestingly, there is no relationship between chronic neuropathic pain and referred sensation although the underlying mechanism of both phenomena is thought to be plasticity in the nervous system as discussed above. However, there is a strong correlation between the amount of cortical reorganisation and magnitude of phantom limb pain. No such correlation was found in non-painful phantom phenomena and it is probable that different neural substrates are responsible (Flor *et al.*, 1995; Flor *et al.*, 2000; Grusser *et al.*, 2001; Knecht *et al.*, 1995) for which genetic factors may be involved (Melzack, 1999). It appears that reorganisation after deafferentation is widespread and probably involves bilateral cerebral structures (Knecht *et al.*, 1995).

Technical limitation of the study

Pain is a subjective experience and always a challenge for clinicians to quantify and objectively evaluate this most common complaint. The description of pain, according to the International Association for the Study of Pain (IASP), is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage and described in terms of such damage". A critical aspect of the IASP's definition is defined

in terms of human experience and therefore many factors, influence communication about pain (Ong and Seymour, 2004). The chronic The measurement of subjective pain intensity is critical for both researchers and clinicians and different clinical and laboratory measurement scales are used for its assessment, and hence it is important that these different methods of measurement need to show similar rates of correct respond by the patients.

A Visual Analogue Scale (VAS) and McGill Pain Questionnaires (MPQ) were used in this study as both were found to be reliable, valid and internally consistent(Campbell, 2003). The VAS scale is simple and reproducible and more sensitive for the measurement of pain intensity and has a greater validity to measure therapeutic effects (Langley and Sheppeard, 1985). The possibility of incorrect responding can be minimised by encouragement, clear instruction and supervision and provides better data in younger patients (Jensen *et al.*, 1986).

Another advantage of the VAS is that pain is measured continuously (Bijur *et al.*, 2003; Gallagher *et al.*, 2002). The VAS is physically awkward for patients who have perceptual/motor problems that preclude making the line with pen and it can be time consuming in a busy clinical setting (Choiniere and Amsel, 1996) but these are minor drawbacks.

It is well recognised that pain is a diverse experience influenced by many factors including personality, past memories of painful events, emotion and culture an this inability of VAS to measure these aspects of patient has been a major criticism of its use (Langley and Sheppeard, 1985).

The McGill pain questionnaires produced by Melzack and Torgerson have been used to quantify clinical pain and efficacy of pain control methods and found to be sensitive, reliable and discriminative instruments (Melzack, 1975; Melzack and Torgerson, 1971). However their major draw backs include the need for an understanding of its fairly sophisticated, vocabulary (Flaherty, 1996). They are used more often as diagnostic tools rather than as methods for measuring a therapeutic trial (Ong and Seymour, 2004).

QST is currently being used to detect and characterise loss of sensation, and allodynia and hyperalgesia (Dotson, 1997; Dyck and O'Brien, 2002; Shy *et al.*, 2003).It provides a means of assessing the integrity of myelinated and unmyelinated sensory fibres in periphery and central nococeptive pathways in patients. QST allows accurate, reproducible assessments of neuropathic pain (Dotson, 1997) as discussed in Chapter VII.

Conclusions

This present study concluded that a novel method of surgical repair- spinal cord re-implantation of avulsed roots could improve pain symptoms associated with severe brachial plexus injury. It appears that after deafferentation, the relationship between plastic changes occurring in the nervous system and chronic neuropathic pain seems to be far more complex than thought and an understanding of the mechanisms involved will help to develop treatment programmes which will improve the management of chronic neuropathic pain. Identification of the neurobiological mechanisms responsible for neuropathic pain may offer a more rational basis for its treatment. It is important to move from an empirical symptom control approach to one which targets the specific mechanism involved in the manifestation of intractable pain syndrome.

Chapter IX: Future work

Repair of the brachial plexus is a very challenging surgical problem but there is no longer a question of the worth of surgical management of such a catastrophic injury which often occurs in otherwise healthy young men resulting in a devastating impact on their lives. Although there are considerable improvements for the outcome of functional recovery in the proximal part of the injured limb following surgical repair, to regain function of distal parts of the limb, restoration of sensory function and management of pain remains a challenging problem and further work needs to be done. Restoration of hand function has remained largely unobtainable following avulsion injury due to the prolonged time require for nerve regeneration. By the time the regenerated nerve reaches the target organ i.e. muscle, it is already fibrosed (Terzis *et al.*, 2001). Reinnervation of hand muscles was however, described after a complete brachial plexus avulsion injury with spinal cord replantation in a child (Carlstedt *et al* 2004). After complete brachial plexus lesion, the shortage of a donor nerve for neurotization is a major problem for surgical repair to regain function even for proximal limb. This study demonstrates that this problem can be overcome by novel surgical methods of re-implantation combined with well established surgical measures such as graft and neurotization by nerve transfer. Although muscle function was restored following re-implantation, the outcome was hampered by co-contraction and hence further work needs to be performed to address this problem.

Over the past two decades, techniques for the repair of injury to the brachial plexus have evolved steadily; however, procedures currently seem to have a plateau (Bentolila *et al.*, 1999). In addition, it is now realised that treatment of nerve injury is not merely a mechanical problem but an extremely complex biological problem and therefore in the laboratory environment, interest has shifted from primarily focusing on surgical repair techniques to basic biological mechanisms regulating and influencing key factors such as post traumatic neural death (Bergerot *et al* 2004).

Since peripheral nerve repair technique cannot be further refined at present, there is a need for new strategies to address these issues. It appears that additional advances can be made through scientific research on the pathophysiology of nerve tissue and pharmaceutical agents that facilitate nerve growth (Blesch *et al.*, 2002; Blits *et al.*, 1999; Carlstedt and Noren, 1995).

It is also now well established that there is a re-organisation of the nervous system as a consequence of peripheral nerve injury because the peripheral and central nervous

systems are not only anatomically but also functionally integrated. The re-organisation of the nervous system plays an important role in sensory and pain phenomena and hence it is important to expand our understanding of re-organisation in order to rehabilitate the paralysed arm and to improved pain relief. Pain following brachial plexus injury in adult can be so intense and so much so that paralysis becomes a secondary concern for the patient as well as the physician's perspective for treating the injury. There was excellent restoration of sensation and lack of the long term central pain of avulsion injury, observed in a child with obstetric brachial plexus injury (Anand and Birch, 2002). Functional neuroimaging and physiological studies of adults and neonates with brachial plexus injuries may reveal differences of nervous system plasticity and these studies could indicate novel strategies to improve sensory function and relieve pain.

In addition, to address the above problems, lack of agreement remains among experienced peripheral nerve surgeons regarding management of brachial plexus injury (Belzberg, 2004) and there is also little agreement about methods to measure its outcome (Birch, 2001; Eggers and Mennen, 2001).These disagreements are likely to persist until prospective randomised studies are conducted to determine the relative merits of various treatments. In future, such studies should be done with agreed methods to measure outcome.

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Appendix 1
ISRT (Brachial Plexus Injury) Study
The Royal National Orthopaedic Hospital & Hammersmith Hospital

Name: _____ D.O.B: _____
Address 1: _____ Unit No: _____
_____ Sex: M/F
_____
Address 2: _____

_____
_____
Telephone: _____
E-Mail: _____

Referring Hospital: _____
Referring Doctor: _____
GP: _____

Cause of Injury: Date of Injury: _____
Age at the time of Injury:
Limb dominance: _____ Limb Injured: _____
Occupation before injury:
Occupation after injury:
Duration of away from the work:

Date of first seen:
Date of first operation:
Date of second operation:
Date of third and further operation:
Date of Rehabilitation:

Date of the study:	RNOH	Hammersmith
Visit 1		
Visit 2		
Visit 3		
Visit 4		

Consent:

Associated Injury

Head:

Spine:

Chest:

Abdomen:

Pelvis:

Vascular:

Fractures:

Injury score:

Other associated medical illness:

Clinical findings at the time of injury:

Horner's syndrome:
Diaphragm:

Investigations:

Histamine:

MRI:

CT:
- Head:
- Spine:
- Body:

CT Myelogram:
Myelogram:
Angiography:
X ray diaphragm:
X ray relevant fracture:

Intra-operative Neurophysiological study:

SEPs		*Distal motor response*
C4		
C5		
C6		
C7		
C8		
T1		
Phrenic Nerve		
Acc Phrenic N		

Intra-operative findings:

	C4	C5	C6	C7	C8	T1
Rupture						
Avulsion						
L I C						
Intact						

Other associated nerve injury:

Anatomical variant:

Repair
Neurolysis ulnar nerve:
Standard Graft C5:
Standard Graft C6:
Standard Graft C7:
Standard Graft C8:
Standard Graft T1:
Accessory to Suprascapular:
Intercostal to MC:
Intercostal to Lateral Cord:
Intercostal to Median N:
Intercostal to Ulnar N:
Other transfers:

Direct suture:

Transfer of one nerve to another:

Replant:

Other reconstructions:

Other any important details of the operation:

Examination (Injury side):
Co- contraction:
Breathing arm:

Date:						
Trapezius						
Rhomboids						
Serratus A						
P.Maj. Cla						
P.Maj. Ste						
Supraspinatus						
Infraspinatus						
Latissimus D						
Teres Maj						
Deltoid						
Biceps						
Triceps						
Brachioradialis						
E. Car. Rad. L						
Supinator						
E. Car. Ulnaris						
E. Digitorun						
Abd. P. Long						
Ext. P. Long						
Ext. P. Brev						
Pronator teres						
Flex. Car. Rad						
Flex. Dig. Sup						
Flex.Dig.Prof						
Flex.Pol. Long						
APB						
Opp. Poll						
1st Lumbricals						
Flex.C Uln						
Flex.Dig.Prof						
ADM						
1st Dig. minimi						
1st DIO						
Add.Poll						
Wrist Flexors						
Wrist Ext						
Finger Flexors						
Finger Ext						

Reflexes:
Biceps:
Triceps:
Supinator

Arm circumference

Date					
Right					
Left					

Forearm circumference

Date					
Right					
Left					

Sensory examination:

Cotton wool:

Date					
Face					
C3					
C4					
C5					
C6					
C7					
C8					
T1					
T2					
T3					
T4					
T5					
T6					

Referral sensations:

Pinprick:

Date					
Face					
C3					
C4					
C5					
C6					
C7					
C8					
T1					
T2					
T3					
T4					
T5					
T6					

Referral sensations:

Joint Position Sensation:

Date					
Fingers					
Wrist					
Elbow					
Shoulder					

Tinel's sign:

Date					
Median					
Ulnar					
Radial					
Supraclavicular					
Other					

Other Physical Findings:

Range of movement:

Date								
Shoulder	Forward Flexion	Active						
		Passive						
	Lateral Rotation	Active						
		Passive						
	Medial Rotation	Active						
		Passive						
	Abduct-ion	Active						
		Passive						
Elbow		Active						
		Passive						
Forearm	Pronation	Active						
		Passive						
	Supination	Active						
		Passive						
Wrist	Flexion	Active						
		Passive						
	Extension	Active						
		Passive						
Fingers	Flexion	Active						
		Passive						
	Extension	Active						
		Passive						

Functional Outcome (NARAKAS):

Date	Peri-op					
Shoulder						
Elbow						
Forearm						
Wrist						
Fingers						

Pain assessment

Any pain since injury:

Time of onset: (relative to injury)
Immediately .....
Within 24 hours .....
Within 2 weeks.....
Within 6 weeks.....
Within 3 months.....
Within 6 months.....
Over 6 months.....

Pain description such as crushing, burning etc:

Constant pain:
Episodic pain:

Shooting pain on the top of the constant pain:

Site of the pain:
(With date)

Compares with other pains such as broken limbs, tooth ache, birth etc

Visual analog scale

Lowest:
Highest:

Pain score at present:
Date:_____ No Pain _____Worst Imagined pain
Date:_____ No Pain _____Worst Imagined pain
Date:_____ No Pain _____Worst Imagined pain
Date:_____ No Pain _____Worst Imagined pain
Date:_____ No Pain _____Worst Imagined pain
Date:_____ No Pain _____Worst Imagined pain
Relieving/exacerbating such as:
Cold
Illness
Medication
Physio
TENS
Others:

Hyperalgesia:

Phantom sensation:
N.B. Time, course, periodicity, relation to pain, sleep, dreaming, exercise, vision etc.

The worst time of the pain:

Did the pain interfere with:	Sleep	Y	N
	Work or study	Y	N
	Hobbies	Y	N
	Daily activities	Y	N

Medications:

	Dose	Started	Stopped	S/E
Carbamazepine:				
Gabapentin:				
Topiramate:				
Phenytoin:				
Amitriptyline:				
Clonazepam:				
Cannabanoids:				
Morphine:				
Codine:				
NSAIDs:				

Mc Gill Pain Questionnaire

Date					
1	Flickering Quivering Pulsing Throbbing Beating Pounding	8	Tingling Itchy Smarting Stinging	15	Wretched Binding
2	Jumping Flashing Shooting	9	Dull Sore Hurting Aching Heavy	16	Annoying Troublesome Miserable Intense Unbearable
3	Pricking Boring Drilling Stabbing Lancinating	10	Tender Taut Rasping Splitting	17	Spreading Radiating Piercing
4	Sharp Cutting Lacerating	11	Tiring Exhausting	18	Tight Numb Drawing Squeezing Tearing
5	Pinching Pressing Gnawing Cramping Crushing	12	Sickening Suffocating	19	Cool Cold Freezing
6	Tugging Pulling Wrenching	13	Fearful Frightful Terrifying	20	Nagging Nauseating Agonising Dreadful Torturing
7	Hot Burning Scalding Searing	14	Punishing Grueling Cruel Vicious Killing		PPI 0 No Pain 1 Mild 2 Discomforting 3 Distressing 4 Horrible 5 Excruciating
	BRIEF MOMENTARY TRANSIENT		RHYTHEMIC PERIOD INTERMITTENT		CONTANUOUS STEADY CONSTANT

Clinical observation and Neurophysiological assessment at Hammersmith hospital

Von Frey's hair test:

Date						
C4						
C5						
C6						
C7						
C8						
T1						
T2						
T3						
T4						
T5						
T6						

Remarks:

Vibration test:

Date						
Finger						
Wrist						
Elbow						
Shoulder						

Horner's syndrome: Y N Partial Complete

Sweat test:

Date						
Right						
Left						

Thermal Threshold

Date:

	Cold threshold	Warm threshold	Cold pain	Warm pain
C4				
C5				
C6				
C8				
C8				
T1				
T2				
Chest wall				

Remarks:

Date:

	Cold threshold	Warm threshold	Cold pain	Warm pain
C4				
C5				
C6				
C8				
C8				
T1				
T2				
Chest wall				

Remarks:

Date:

	Cold threshold	Warm threshold	Cold pain	Warm pain
C4				
C5				
C6				
C8				
C8				
T1				
T2				
Chest wall				

Remarks:

Summary of Thermal Threshold Findings

Date							
C4	CT						
	WT						
	CP						
	WP						
C5	CT						
	WT						
	CP						
	WP						
C6	CT						
	WT						
	CP						
	WP						
C7	CT						
	WT						
	CP						
	WP						
C8	CT						
	WT						
	CP						
	WP						
T1	CT						
	WT						
	CP						
	WP						
T2	CT						
	WT						
	CP						
	WP						
Chest wall	CT						
	WT						
	CP						
	WP						

EMG Examination:

Date:

	Spontaneous activities	**MUP analysis**	**Recruitment**	**Remarks**
Deltoids				
Pectorals				
Biceps				
Triceps				

Co-contraction:

Breathing arm:

Magnetic Stimulation Test

	Right		Left		
Muscles	Amp	Lat	Amp	Lat	Stimulus
Biceps					
Triceps					
Other					

Discussion/ Models/ Plans